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Requester's Full Name: SABINA GARCIA Examiner #: 74141 Date: 2/10/06
 Art Unit: 1616 Phone Number 301 206 222 Serial Number: 10/520,360
 Mail Box and Bldg/Room Location: 4A45 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

 Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Julie Kay Bush
Crystalline 2,5 Dione
 Inventors (please provide full names):

Earliest Priority Filing Date: 60/315,776 7/12/02 PCT/US2003/9548

For Sequence Searches Only Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number. 7/8/2002

Please search for the compound of cl 1
 and method of use

FB

Please see attached sheet.

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Type of Search

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Searcher: _____	NA Sequence (#) _____	STN _____
Searcher Phone #: _____	AA Sequence (#) _____	Dialog _____
Searcher Location: _____	Structure (#) _____	Questel/Orbit _____
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Date Completed: _____	Litigation _____	Lexis/Nexis _____
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Online Time _____	Other _____	Other (specify) _____

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STRUCTURE FILE UPDATES: 6 MAR 2006 HIGHEST RN 876011-49-3
DICTIONARY FILE UPDATES: 6 MAR 2006 HIGHEST RN 876011-49-3

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TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

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* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
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* available and contains the CA role and document type information. *
*

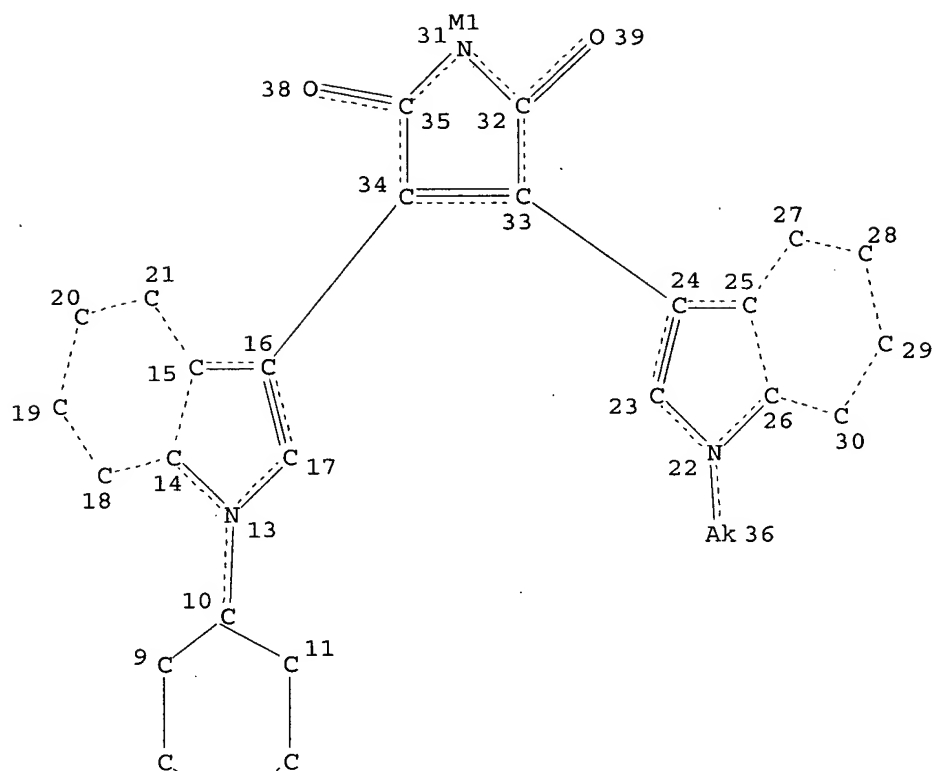
Structure search iteration limits have been increased. See HELP SLIMITS
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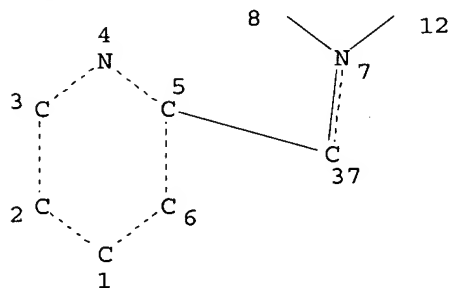
<http://www.cas.org/ONLINE/UG/regprops.html>

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Page 1-A



Page 2-A

NODE ATTRIBUTES:

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NSPEC IS C AT 38
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CONNECT IS E1 RC AT 36
DEFAULT MLEVEL IS ATOM
MLEVEL IS CLASS AT 36 37 38 39
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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NUMBER OF NODES IS 39

STEREO ATTRIBUTES: NONE

L7 4 SEA FILE=REGISTRY SSS FUL L5/

100.0% PROCESSED 639 ITERATIONS
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4 ANSWERS

FILE 'CAPLUS' ENTERED AT 16:38:45 ON 07 MAR 2006
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L9 54 L7

=> dup rem l9

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PROCESSING COMPLETED FOR L9

L10 32 DUP REM L9 (22 DUPLICATES REMOVED)
ANSWERS '1-22' FROM FILE CAPLUS
ANSWERS '23-27' FROM FILE USPATFULL
ANSWERS '28-29' FROM FILE DRUGU
ANSWERS '30-31' FROM FILE BIOSIS
ANSWER '32' FROM FILE PROUSDDR

=> d ibib ed abs hitstr 1-27; d iall 28-32

L10 ANSWER 1 OF 32 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2005:1123756 CAPLUS
DOCUMENT NUMBER: 143:379813
TITLE: Protein kinase C inhibitors for the treatment of
autoimmune diseases and of transplant rejection
INVENTOR(S): Wagner, Jurgen; Schuler, Walter
PATENT ASSIGNEE(S): Novartis A.-G., Switz.; Novartis Pharma G.m.b.H.
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005097108	A1	20051020	WO 2005-EP3663	20050407
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: GB 2004-8066 A 20040408
GB 2004-14540 A 20040629
GB 2004-22068 A 20041005

OTHER SOURCE(S): MARPAT 143:379813

ED Entered STN: 20 Oct 2005

AB The invention discloses the use of protein kinase C inhibitors, e.g. 3-(1-methyl-1H-indol-3-yl)-4-[1-(piperid-4-yl)-1H-indol-3-yl]pyrrole-2,5-dione, in transplantation and autoimmune diseases.

IT 170364-57-5

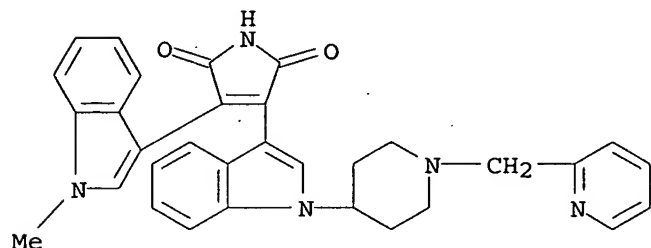
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(protein kinase C inhibitors for treatment of autoimmune diseases and

transplant rejection)

RN 170364-57-5 CAPLUS

CN 1H-Pyrrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-[1-(2-pyridinylmethyl)-4-piperidinyl]-1H-indol-3-yl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 2 OF 32 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 2

ACCESSION NUMBER: 2005:984120 CAPLUS

DOCUMENT NUMBER: 143:279360

TITLE: Methods of detecting CD133 antigen (AC133) expression level and use as biomarker for human cancer diagnosis and therapy monitor

INVENTOR(S): Penning, Maarten Tjerk; Van den Broek, Sebastiaan Johannes Jacobus; Voest, Emile Eugene; Beerepoot, Laurens Victor; Mehra, Niven

PATENT ASSIGNEE(S): Primagen Holding B. V., Neth.; UMC Utrecht Holding B. V.

SOURCE: PCT Int. Appl., 55 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005083123	A1	20050909	WO 2005-NL155	20050302
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
EP 1571225	A1	20050907	EP 2004-75686	20040302
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK			
PRIORITY APPLN. INFO.:			EP 2004-75686	A 20040302
			US 2004-549450P	P 20040302

ED Entered STN: 09 Sep 2005

AB This invention provides methods of detecting CD133 antigen (AC133) expression level and use as a biomarker for human cancer diagnosis and

therapy monitor. Blood anal. including number of circulating endothelial cells and expression levels of human genes AC133 (CD133), EST032 and U1A evaluated by NASBA anal., were determined prior to and during chemotherapy using drugs such as angiostatin or PrimMed01, gemcitabine, and cisplatin, for a wide range of human tumor types. A use of a nucleic acid mol. comprising at least part of a sequence of AC133 or an analog thereof for monitoring a treatment of an individual suffering from a disease is also provided, as well as a diagnostic kit comprising such nucleic acid mol.

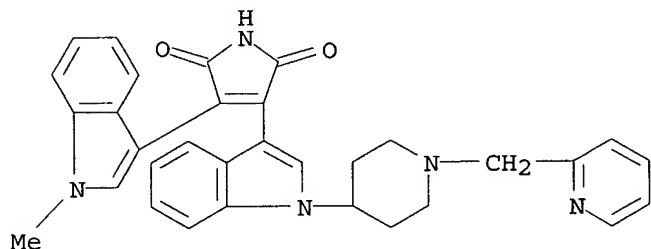
IT 359017-79-1, Enzastaurin hydrochloride 365253-37-8,
LY317615

RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)

(methods of detecting CD133 antigen (AC133) expression level and use as
biomarker for human cancer diagnosis and therapy monitor)

RN 359017-79-1 CAPLUS

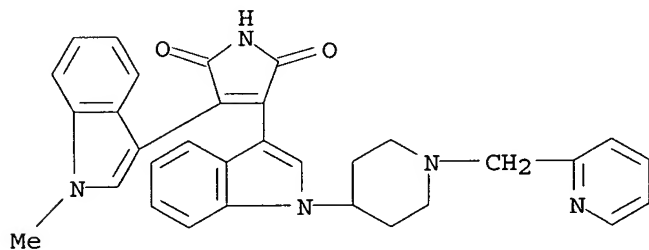
CN 1H-Pyrrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-[1-(2-
pyridinylmethyl)-4-piperidinyl]-1H-indol-3-yl]-, monohydrochloride (9CI)
(CA INDEX NAME)



● HCl

RN 365253-37-8 CAPLUS

CN 1H-Pyrrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-[1-(2-
pyridinylmethyl)-4-piperidinyl]-1H-indol-3-yl]-, dihydrochloride (9CI)
(CA INDEX NAME)



●2 HCl

REFERENCE COUNT:

9

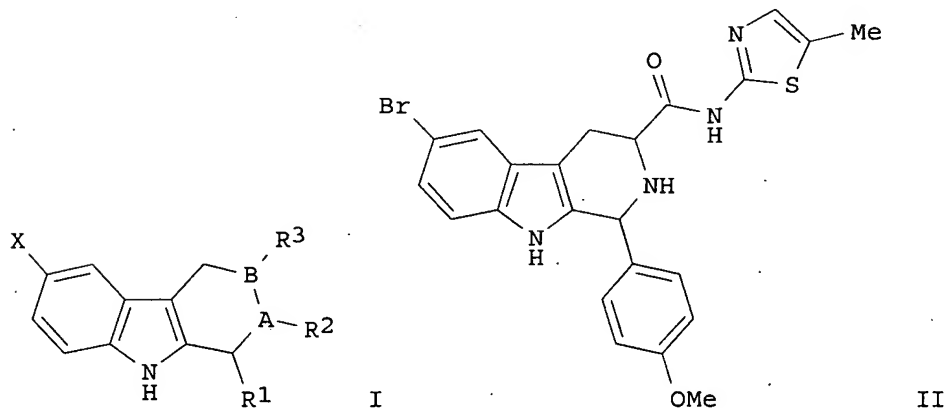
THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 3 OF 32 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 3

ACCESSION NUMBER: 2005:1335317 CAPLUS
 DOCUMENT NUMBER: 144:70000
 TITLE: Preparation of carboline derivatives as antitumor agents
 INVENTOR(S): Moon, Young-Choon; Cao, Liangxian; Tamilarasu, Nadarajan; Qi, Hongyan; Choi, Soongyu; Lennox, William Joseph; Corson, Donald Thomas; Hwang, Seongwoo; Davis, Thomas
 PATENT ASSIGNEE(S): USA
 SOURCE: U.S. Pat. Appl. Publ., 234 pp., Cont.-in-part of U.S. Ser. No. 79,420.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005282849	A1	20051222	US 2005-107783	20050418
US 2005272759	A1	20051208	US 2005-79420	20050315
PRIORITY APPLN. INFO.:			US 2004-552725P	P 20040315
			US 2005-79420	A2 20050315

OTHER SOURCE(S): MARPAT 144:70000
 ED Entered STN: 23 Dec 2005
 GI



AB The title compds. I [X = H, alkyl, haloalkyl, OH, etc.; A = C, N; B = C, N, with the proviso that at least one of A or B = N, and that when A = N, B = C; R1 = OH, alkyl, alkenyl, etc.; R2 = H, OH, 5-10 membered heteroaryl, etc.; R3 = H, COR (wherein R = OH, NH2 which is optionally substituted with cycloalkyl or heteroaryl, (un)substituted 5-10 membered heteroaryl); and their pharmaceutically acceptable salts] that inhibit the expression of VEGF post-transcriptionally and therefore are useful in the inhibition of VEGF production, in the treatment of solid tumor cancer, and in reducing plasma and/or tumor VEGF levels, were prepared E.g., a 2-step synthesis of II, starting from p-anisaldehyde and 5-bromotryptophan, was given. Over 900 exemplified compds. I were tested in assay evaluating their affect on hypoxia-inducible endogenous VEGF expression (biol. data

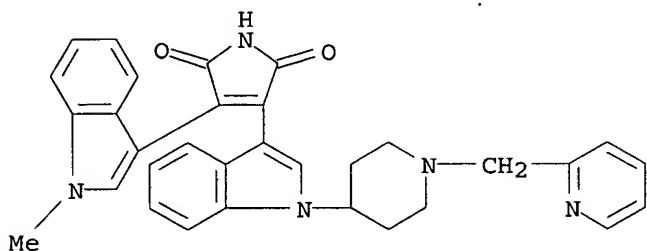
given).

IT 365253-37-8, LY317615

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(co-drug; preparation of carboline derivs. for inhibiting VEGF production)

RN 365253-37-8 CAPLUS

CN 1H-Pyrrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-[1-(2-pyridinylmethyl)-4-piperidinyl]-1H-indol-3-yl]-, dihydrochloride (9CI)
(CA INDEX NAME)



● 2 HCl

L10 ANSWER 4 OF 32 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 4

ACCESSION NUMBER: 2005:303191 CAPLUS

DOCUMENT NUMBER: 142:341966

TITLE: Hydrogels used to deliver medicaments to the eye for the treatment of posterior segment diseases

INVENTOR(S): Schultz, Clyde L.

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 7 pp., Cont.-in-part of U.S. Ser. No. 821,718.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005074497	A1	20050407	US 2004-971997	20041022
US 2005208102	A1	20050922	US 2004-821718	20040409
US 2005255144	A1	20051117	US 2005-102454	20050409
WO 2005110473	A2	20051124	WO 2005-US12185	20050409

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:

US 2003-461354P P 20030409

US 2004-821718

A2 20040409

US 2004-971997

A2 20041022

ED Entered STN: 08 Apr 2005

AB This invention provides a polymeric drug delivery system including a hydrogel containing one or more drugs for the treatment of a posterior segment disease. Exemplary drugs are anti-angiogenesis compds. for the treatment of macular degeneration. Allowing passive transference of this drug from a dilute solution into the hydrogel produces the delivery system. The hydrogel, when placed in contact with the eye, delivers the drug. The delivery of the drug is sustained over an extended period of time, which is of particular utility in the eye, which is periodically flushed with tears. This sustained delivery accelerates the treatment process while avoiding potential damaging effects of localized delivery of high concns. of compds., e.g., from eye drops.

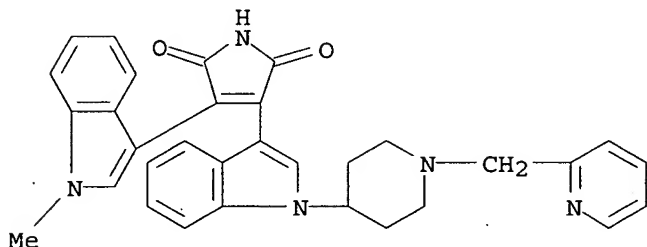
IT 365253-37-8, LY317615

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(hydrogels containing drugs for treatment of eye diseases in posterior segment)

RN 365253-37-8 CAPLUS

CN 1H-Pyrrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-[1-(2-pyridinylmethyl)-4-piperidinyl]-1H-indol-3-yl]-, dihydrochloride (9CI)
(CA INDEX NAME)



● 2 HCl

L10 ANSWER 5 OF 32 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 5

ACCESSION NUMBER: 2005:975665 CAPLUS

DOCUMENT NUMBER: 143:264929

TITLE: Methods for detecting AC133 antigen mRNA for diagnosis and treatment of cancer and other diseases

INVENTOR(S): Penning, Maarten Tjerk; Beerepoot, Laurens Victor; Van Den Broek, Sebastiaan Johannes Jacobus; Mehra, Niven; Voest, Emile Eugene

PATENT ASSIGNEE(S): Primagen Holding B.V., Neth.; UMC Utrecht Holding B.V.

SOURCE: Eur. Pat. Appl., 28 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1571225	A1	20050907	EP 2004-75686	20040302

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 IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK
 WO 2005083123 A1 20050909 WO 2005-NL155 20050302
 W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
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 GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
 LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
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 EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT,
 RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
 MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:

EP 2004-75686

A 20040302

US 2004-549450P

P 20040302

ED Entered STN: 08 Sep 2005

AB The invention provides methods for detecting AC133 antigen mRNA for
 diagnosis and treatment of cancer and other diseases. AC133 antigen mRNA
 may be quantitated by PCR, RT-PCR, NASBA, SDA, TMA, bDNA or rolling circle
 amplification. Diseases include cancer and heart disease, high blood
 pressure, ischemia, stroke, psoriasis, Crohn's disease, rheumatoid
 arthritis, endometriosis, atherosclerosis, obesity, diabetes mellitus,
 diabetic retinopathy, macular degeneration, Alzheimer's disease, Peutz
 Jegher's syndrome, multiple sclerosis, systemic lupus erythematosus,
 Wegener's granulomatosis, vasculitis, sickle cell disease, thalassemia and
 angina.

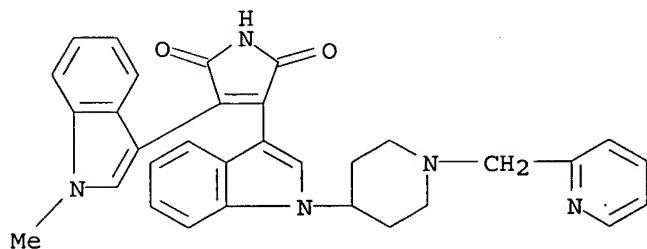
IT 359017-79-1, Enzastaurin hydrochloride 365253-37-8

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
 (Biological study); USES (Uses)

(methods for detecting AC133 antigen mRNA for diagnosis and treatment
 of cancer and other diseases)

RN 359017-79-1 CAPLUS

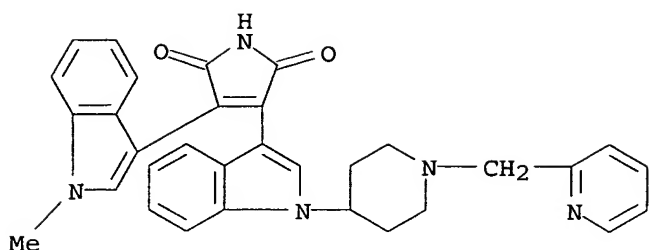
CN 1H-Pyrrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-[1-(2-
 pyridinylmethyl)-4-piperidinyl]-1H-indol-3-yl]-, monohydrochloride (9CI)
 (CA INDEX NAME)



● HCl

RN 365253-37-8 CAPLUS

CN 1H-Pyrrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-[1-(2-
 pyridinylmethyl)-4-piperidinyl]-1H-indol-3-yl]-, dihydrochloride (9CI)
 (CA INDEX NAME)



● 2 HCl

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 6 OF 32 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 6

ACCESSION NUMBER: 2005:761909 CAPLUS

DOCUMENT NUMBER: 143:278624

TITLE: The Protein Kinase C β -Selective Inhibitor, Enzastaurin (LY317615.HCl), Suppresses Signaling through the AKT Pathway, Induces Apoptosis, and Suppresses Growth of Human Colon Cancer and Glioblastoma Xenografts

AUTHOR(S): Graff, Jeremy R.; McNulty, Ann M.; Hanna, Kimberly Ross; Konicek, Bruce W.; Lynch, Rebecca L.; Bailey, Spring N.; Banks, Crystal; Capen, Andrew; Goode, Robin; Lewis, Jason E.; Sams, Lillian; Huss, Karen L.; Campbell, Robert M.; Iversen, Philip W.; Neubauer, Blake Lee; Brown, Thomas J.; Musib, Luna; Geeganage, Sandaruwan; Thornton, Donald

CORPORATE SOURCE: Lilly Research Labs, Eli Lilly and Company, Indianapolis, IN, USA

SOURCE: Cancer Research (2005), 65(16), 7462-7469

CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 15 Aug 2005

AB Activation of protein kinase C β has been repeatedly implicated in tumor-induced angiogenesis. The PKC β -selective inhibitor, Enzastaurin (LY317615.HCl), suppresses angiogenesis and was advanced for clin. development based upon this antiangiogenic activity. Activation of PKC β has now also been implicated in tumor cell proliferation, apoptosis, and tumor invasiveness. Herein, we show that Enzastaurin has a direct effect on human tumor cells, inducing apoptosis and suppressing the proliferation of cultured tumor cells. Enzastaurin treatment also suppresses the phosphorylation of GSK3 β ser9, ribosomal protein S6S240/244, and AKTThr308. Oral dosing with Enzastaurin to yield plasma concns. similar to those achieved in clin. trials significantly suppresses the growth of human glioblastoma and colon carcinoma xenografts. As in cultured tumor cells, Enzastaurin treatment suppresses the phosphorylation of GSK3 β in these xenograft tumor tissues. Enzastaurin treatment also suppresses GSK3 β phosphorylation to a similar extent in peripheral blood mononuclear cells (PBMCs) from these treated mice. These data show that Enzastaurin has a direct antitumor effect and that Enzastaurin treatment suppresses GSK3 β phosphorylation in both tumor

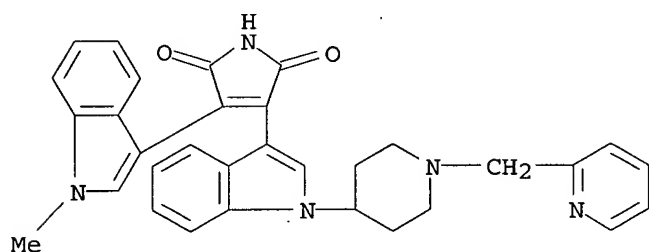
tissue and in PBMCs, suggesting that GSK3 β phosphorylation may serve as a reliable pharmacodynamic marker for Enzastaurin activity. With previously published reports, these data support the notion that Enzastaurin suppresses tumor growth through multiple mechanisms: direct suppression of tumor cell proliferation and the induction of tumor cell death coupled to the indirect effect of suppressing tumor-induced angiogenesis.

IT 170364-57-5, Enzastaurin

RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(protein kinase C β -selective inhibitor, Enzastaurin (LY317615.HCl), suppresses signaling through the AKT pathway, induces apoptosis, and suppresses growth of human colon cancer and glioblastoma xenografts)

RN 170364-57-5 CAPLUS

CN 1H-Pyrrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-[1-(2-pyridinylmethyl)-4-piperidinyl]-1H-indol-3-yl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 7 OF 32 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 7

ACCESSION NUMBER: 2004:60317 CAPLUS

DOCUMENT NUMBER: 140:117402

TITLE: Crystalline 3-(1-methyl-1H-indol-3-yl)-4-[1-(pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole-2,5-dione monohydrochloride preparation for antitumor pharmaceuticals

INVENTOR(S): Bush, Julie Kay; Faul, Margaret Mary; Reutzel-Edens, Susan Marie

PATENT ASSIGNEE(S): Eli Lilly and Company, USA

SOURCE: PCT Int. Appl., 27 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

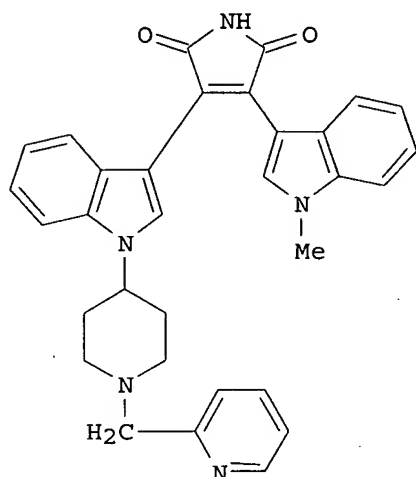
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004006928	A1	20040122	WO 2003-US19548	20030708
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,				

KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
 FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
 BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2393720	AA	20040116	CA 2002-2393720	20020716
AU 2003280958	A1	20040202	AU 2003-280958	20030708
EP 1523313	A1	20050420	EP 2003-742111	20030708
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2006502115	T2	20060119	JP 2004-521470	20030708
US 2005288332	A1	20051229	US 2005-520360	20050105
NO 2005000676	A	20050209	NO 2005-676	20050209
PRIORITY APPLN. INFO.:			US 2002-395976P	P 20020712
			WO 2003-US19548	W 20030708

ED Entered STN: 26 Jan 2004
 GI



AB The present invention relates to crystalline I monohydrochloride salt, a pharmaceutical formulation containing said salt and to methods for treating cancer and for inhibiting tumor growth using said salt. I was prepared, converted to the monohydrochloride, formulated into capsules and was effect in treating cancer and inhibiting tumor growth.

IT 170364-57-5P 359017-79-1P 647031-15-0P

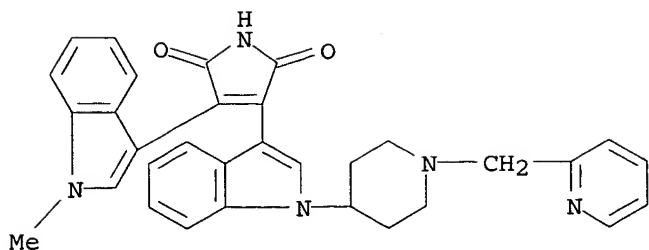
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(crystalline

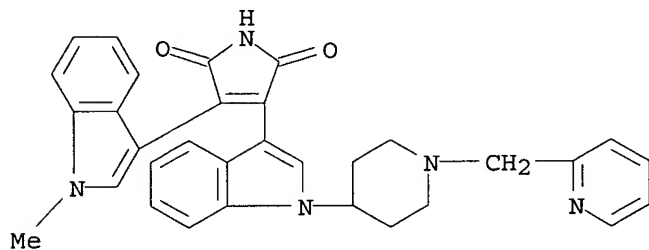
3-(1-methyl-1H-indol-3-yl)-4-[1-(pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole-2,5-dione monohydrochloride preparation for antitumor pharmaceuticals)

RN 170364-57-5 CAPLUS

CN 1H-Pyrrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-[1-(2-pyridinylmethyl)-4-piperidinyl]-1H-indol-3-yl]- (9CI) (CA INDEX NAME)



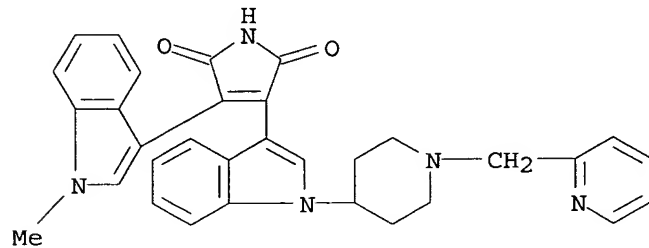
RN 359017-79-1 CAPLUS

CN 1H-Pyrrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-[1-(2-pyridinylmethyl)-4-piperidinyl]-1H-indol-3-yl]-, monohydrochloride (9CI)
(CA INDEX NAME)

● HCl

RN 647031-15-0 CAPLUS

CN 1H-Pyrrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-[1-(2-pyridinylmethyl)-4-piperidinyl]-1H-indol-3-yl]-, monohydrochloride, monohydrate (9CI) (CA INDEX NAME)



● HCl

● H₂O

REFERENCE COUNT:

4

THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS

Searched by Barb O'Bryen, STIC 2-2518

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 8 OF 32 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 8

ACCESSION NUMBER: 2003:1000293 CAPLUS

DOCUMENT NUMBER: 141:116579

TITLE: LY317615 decreases plasma VEGF levels in human tumor xenograft-bearing mice

AUTHOR(S): Keyes, Kristan A.; Mann, Larry; Sherman, Michael; Galbreath, Elizabeth; Schirtzinger, Linda; Ballard, Darryl; Chen, Yun-Fei; Iversen, Philip; Teicher, Beverly A.

CORPORATE SOURCE: Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN, 46285, USA

SOURCE: Cancer Chemotherapy and Pharmacology (2004), 53(2), 133-140

CODEN: CCPHDZ; ISSN: 0344-5704

PUBLISHER: Springer-Verlag

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 23 Dec 2003

AB Angiogenesis plays an important role in tumor growth. Angiogenic growth factors may be useful as biomarkers of antiangiogenic activity since their plasma concns. correlate with the efficacy of treatments directed toward angiogenic targets. SW2 small-cell lung carcinoma (SCLC), Caki-1 renal cell carcinoma and HCT-116 colon carcinoma tumors produce measurable plasma VEGF, bFGF and TGF β in nude mice. Mice bearing these human tumor xenografts were treated orally twice daily with the PKC β inhibitor, LY317615 (days 14 - 30 for SW2 and HCT116, and days 21 - 39 for Caki-1). Plasma was collected every 3 days from control and treated mice. LY317615 significantly decreased plasma VEGF levels in mice bearing SW2 SCLC and Caki-1 renal cell carcinoma compared to control plasma concns. beginning 5 - 7 days after initiating therapy. VEGF plasma levels remained suppressed after termination of LY317615 treatment and for the duration of the study (an addnl. 2 to 3 wk). Plasma VEGF levels in mice bearing HCT116 xenografts were not altered by LY317615 treatment and plasma bFGF and TGF- β were not altered by LY317615 in any of the animals. As shown by CD31 immunohistochem. staining, LY317615 decreased intratumoral vessel d. by nearly 40% in all three tumors. Only the Caki-1 tumor responded to single-agent LY317615 therapy with a measurable tumor growth delay. Thus, unexpectedly inhibition of PKC β in vivo led to decreased VEGF production that persisted after therapy as well as to decreased intratumoral vessels. Plasma VEGF was a weak marker of response to LY317615, and plasma bFGF and TGF β were not markers of LY317615 activity.

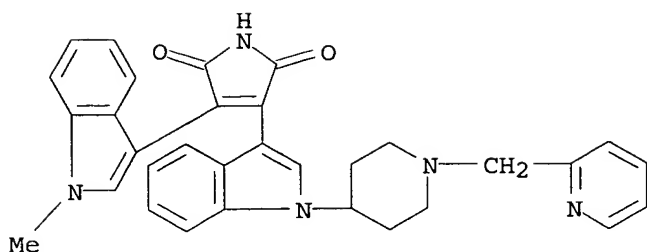
IT 365253-37-8, LY317615

RL: DMA (Drug mechanism of action); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(LY317615 decreases plasma VEGF levels in human tumor xenograft-bearing mice)

RN 365253-37-8 CAPLUS

CN 1H-Pyrrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-[1-(2-pyridinylmethyl)-4-piperidinyl]-1H-indol-3-yl]-, dihydrochloride (9CI) (CA INDEX NAME)



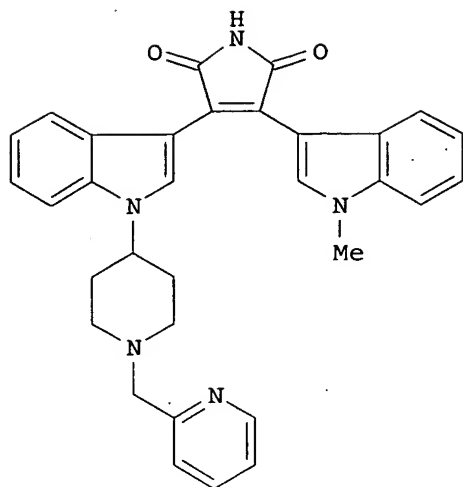
● 2 HCl

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 9 OF 32 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 9
 ACCESSION NUMBER: 2002:31257 CAPLUS
 DOCUMENT NUMBER: 136:79750
 TITLE: Therapeutic treatment of cancer with a protein kinase C inhibitor
 INVENTOR(S): Teicher, Beverly Ann; Ways, Douglas Kirk
 PATENT ASSIGNEE(S): Eli Lilly and Company, USA
 SOURCE: PCT Int. Appl., 28 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002002116	A2	20020110	WO 2001-US16502	20010628
WO 2002002116	A3	20020523		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: US 2000-215172P P 20000629
 ED Entered STN: 11 Jan 2002
 GI



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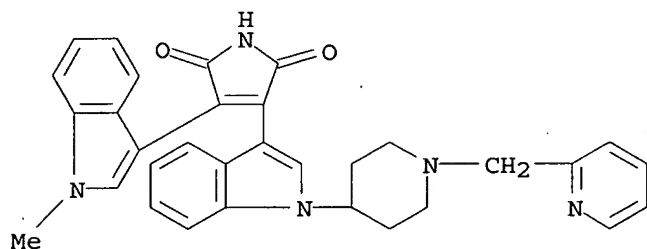
AB Methods are disclosed for treating cancer and inhibiting tumor growth by administering to a mammal in need thereof a therapeutically effective amount of I, or a pharmaceutically acceptable salt or solvate thereof.

IT 170364-57-5

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(indolylpyrroledione derivative protein kinase C inhibitor for cancer treatment)

RN 170364-57-5 CAPLUS

CN 1H-Pyrrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-[1-(2-pyridinylmethyl)-4-piperidinyl]-1H-indol-3-yl]- (9CI) (CA INDEX NAME)



L10 ANSWER 10 OF 32 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 10

ACCESSION NUMBER: 2002:31235 CAPLUS

DOCUMENT NUMBER: 136:90969

TITLE: Use of a protein kinase C inhibitor to enhance the clinical efficacy of anti-neoplastic chemotherapeutic agents and radiation therapy

INVENTOR(S): Teicher, Beverly Ann; Ways, Douglas Kirk

PATENT ASSIGNEE(S): Eli Lilly and Company, USA

SOURCE: PCT Int. Appl., 30 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002002094	A2	20020110	WO 2001-US16490	20010625
WO 2002002094	A3	20030116		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			

PRIORITY APPLN. INFO.:

US 2000-215043P

P 20000629

ED Entered STN: 11 Jan 2002

AB Methods are disclosed for treating a neoplasm which comprises administering to a mammal in need thereof, an anti-neoplastic agent or therapeutic radiation in combination with 3-[1-(1-(pyridin-2-ylmethyl)piperidin-4-yl)-indol-3-yl]-4-(1-methylindol-3-yl)-1-pyrrole-2,5-dione (I) or a pharmaceutically acceptable salt or solvate thereof, and for enhancing the anti-neoplastic effect of anti-neoplastic agents or therapeutic radiation which comprises administering to a mammal in need thereof, I in combination with said anti-neoplastic agent or said therapeutic radiation having an anti-neoplastic effect. A series of anti-neoplastic agents is claimed. A capsule contained active agents 250, starch 200, and magnesium stearate 10 mg.

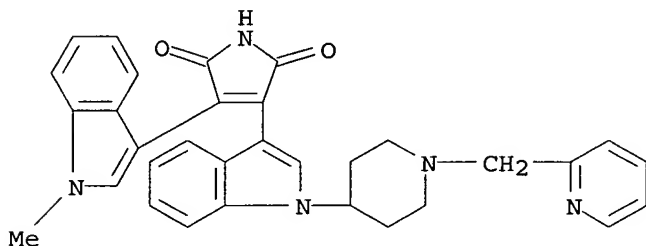
IT 170364-57-5

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(use of protein kinase C inhibitor to enhance clin. efficacy of anti-neoplastic chemotherapeutic agents and radiation therapy)

RN 170364-57-5 CAPLUS

CN 1H-Pyrrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-[1-(2-pyridinylmethyl)-4-piperidinyl]-1H-indol-3-yl]- (9CI) (CA INDEX NAME)



L10 ANSWER 11 OF 32 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 11

ACCESSION NUMBER: 2002:779637 CAPLUS

DOCUMENT NUMBER: 138:32965

TITLE: An in vitro tumor model: analysis of angiogenic factor expression after chemotherapy

AUTHOR(S): Keyes, Kristan; Cox, Karen; Treadway, Patti; Mann, Larry; Shih, Chuan; Faul, Margaret M.; Teicher, Beverly A.

CORPORATE SOURCE: Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN, 46285, USA

SOURCE: Cancer Research (2002), 62(19), 5597-5602

CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

ED Entered STN: 13 Oct 2002

AB Tumor tissues include malignant cells and a stroma made up of mainly inflammatory cells, endothelial cells, and fibroblasts. To differentiate the effects of treatment on angiogenic cytokine secretion in tumor tissue, exponential and stationary phase human CaKi-1 renal cell carcinoma cells, human SW2 small cell lung carcinoma cells, human umbilical vein endothelial cells (HUVECs), murine NIH-3T3 fibroblasts, and murine RAW264.7 macrophages were exposed to gemcitabine, paclitaxel, carboplatin, and the protein kinase C β inhibitor LY317615, and secretion (24 h) of tumor necrosis factor- α , basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), and transforming growth factor (TGF)- β was determined by a Luminex FlowMetrix assay. After 72 h of exposure, exponential RAW, 3T3, and SW2 cells were sensitive to gemcitabine; exponential and stationary SW2 and HUVECs were sensitive to paclitaxel; and exponential and stationary HUVECs were most sensitive to LY317615. None of the cells secreted detectable tumor necrosis factor- α . Generally, exponential cells secreted higher levels of cytokines than stationary cells (stationary cells secreted approx. 10 times less TGF- β). Only malignant cells secreted VEGF (80-300 pg/106 cells). VEGF secretion by exponential SW2 cells decreased in an anticancer agent concentration-dependent manner. Every cell type secreted TGF- β (40-700 pg/106 cells). Exponential 3T3, RAW, CaKi-1, and SW2 cells secreted the most TGF- β , and levels did not decrease with treatment. Only CaKi-1, SW2, and HUVECs secreted bFGF (0.5-50 pg/106 cells). CaKi-1 cells increased secretion of bFGF with therapy. Although malignant cells alone secreted VEGF, stromal cells secreted TGF- β and bFGF at levels comparable with or greater than malignant cells and thus may be important contributors to tumor growth and progression.

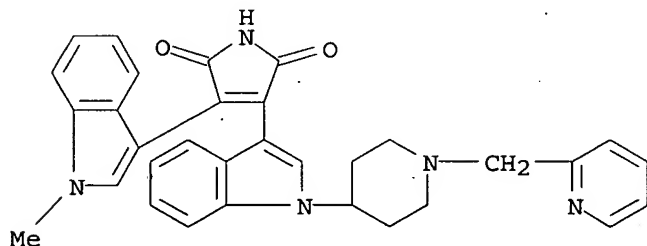
IT 365253-37-8, LY317615

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(angiogenic factor and cytokine expression in cancer and non-cancer cells after chemotherapy)

RN 365253-37-8 CAPLUS

CN 1H-Pyrrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-[1-(2-pyridinylmethyl)-4-piperidinyl]-1H-indol-3-yl]-, dihydrochloride (9CI)
(CA INDEX NAME)



● 2 HCl

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 12 OF 32 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 12

ACCESSION NUMBER: 2002:512394 CAPLUS

DOCUMENT NUMBER: 138:247991

TITLE: Antiangiogenic and Antitumor Effects of a Protein Kinase C β Inhibitor in Human Breast Cancer and Ovarian Cancer Xenografts

AUTHOR(S): Teicher, Beverly A.; Menon, Krishna; Alvarez, Enrique; Shih, Chuan; Faul, Margaret M.

CORPORATE SOURCE: Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN, 46285, USA

SOURCE: Investigational New Drugs (2002), 20(3), 241-251
CODEN: INNDDK; ISSN: 0167-6997

PUBLISHER: Kluwer Academic Publishers

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 10 Jul 2002

AB In cell culture, the compound 317615·2HCl, a potent inhibitor of VEGF-stimulated HUVEC proliferation, was not very effective against MX-1 breast cancer cells (IC₅₀ = 8.1 μ M) or SKOV-3 ovarian carcinoma cells (IC₅₀ = 9.5 μ M). Exposure to combinations of paclitaxel or carboplatin and 317615·2HCl with MX-1 cells in culture resulted in cell survival that reflected primarily additivity of the 2 agents. Exposure of SKOV-3 cells to paclitaxel or carboplatin along with 317615·2HCl resulted in cell survivals that reflected additivity of 317615·2HCl with paclitaxel and greater-than-additive cytotoxicity with carboplatin. Administration of 317615·2HCl orally twice daily to nude mice bearing s.c. MX-1 tumors or SKOV-3 tumors resulted in a decreased number of intratumoral vessels as determined by CD31 and CD105 staining with decreases of 35% and 43% in MX-1 tumors and 60% and 75% in SKOV-3 tumors, resp. 317615·2HCl was an active antitumor agent against the MX-1 xenograft and increased the tumor growth delay produced by paclitaxel by 1.7-fold and the tumor growth delay produced by carboplatin by 3.8-fold. Administration of 317615·2HCl also increased the tumor growth delay produced by fractionated radiation therapy in the MX-1 tumor. Treatment with 317615·2HCl alone increased the lifespan of animals bearing i.p. SKOV-3 xenografts by 1.9 fold compared with untreated control animals. The combination of paclitaxel and 317615·2HCl resulted in 100% 120-day survival of SKOV-3 bearing animals. Administration of 317615·2HCl along with carboplatin to animals bearing the SKOV-3 tumor produced a 1.8-fold increase in lifespan compared with carboplatin alone. 317615·2HCl is a promising new antiangiogenic agent that is in early phase clin. testing.

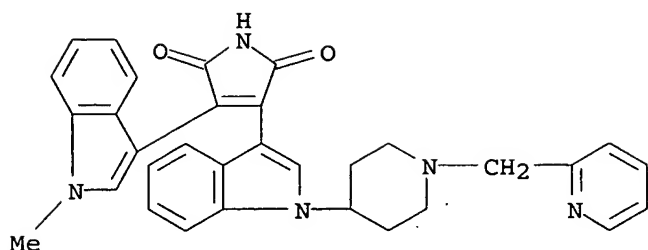
IT 365253-37-8

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(antiangiogenic and antitumor effects of a protein kinase C β inhibitor in human breast cancer and ovarian cancer xenografts)

RN 365253-37-8 CAPLUS

CN 1H-Pyrrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-[1-(2-pyridinylmethyl)-4-piperidinyl]-1H-indol-3-yl]-, dihydrochloride (9CI)
(CA INDEX NAME)



● 2 HCl

REFERENCE COUNT: 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 13 OF 32 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 13

ACCESSION NUMBER: 2001:914698 CAPLUS

DOCUMENT NUMBER: 137:288547

TITLE: Antiangiogenic effects of a protein kinase C β -selective small molecule

AUTHOR(S): Teicher, Beverly A.; Alvarez, Enrique; Menon, Krishna; Esterman, Michail A.; Considine, Eileen; Shih, Chuan; Faul, Margaret M.

CORPORATE SOURCE: Lilly Corporate Center, Lilly Research Laboratories, Indianapolis, IN, 46285, USA

SOURCE: Cancer Chemotherapy and Pharmacology (2002), 49(1), 69-77

CODEN: CCPHDZ; ISSN: 0344-5704

PUBLISHER: Springer-Verlag

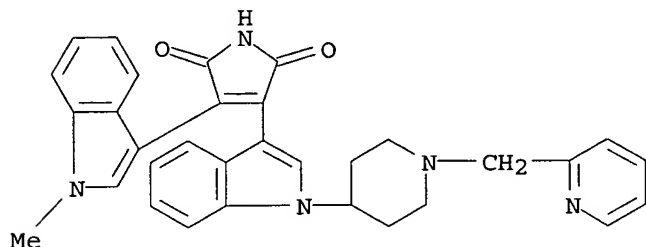
DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 19 Dec 2001

AB Protein kinase C frequently plays a central role in the intracellular signal transduction of growth factors and cytokines. The acyclic bisindolylmaleimide 317615·2HCl was identified as a potent selective inhibitor of protein kinase C β . The compound 317615·2HCl was tested in culture and in vivo in the rat corneal micropocket and in the SW2 small-cell lung carcinoma human tumor xenograft. In cell culture, 317615·2HCl was a more potent inhibitor of VEGF-stimulated HUVEC proliferation (IC₅₀ 150 nM, 72 h) than of human SW2 small-cell lung carcinoma cell proliferation (IC₅₀ 3.5 μ M, 72 h). When administered orally twice daily for 10 days, the compound 317615·2HCl markedly decreased the neo-angiogenesis induced by VEGF or bFGF in the rat corneal micropocket assay. To assess antitumor efficacy, 317615·2HCl was administered orally twice daily to nude mice bearing SW2 xenograft tumors on days 14 through 30 after tumor implantation. The number of countable intratumoral vessels was decreased in a dose-dependent manner reaching as low as one-quarter the number in the control tumors. The decrease in intratumoral vessels was paralleled by increases in tumor growth delay. Treatment of the tumor-bearing animals with paclitaxel or carboplatin followed by treatment with 317615·2HCl resulted in a 2.5- to 3.0-fold increase in tumor growth delay compared with the standard chemotherapeutic agents alone. 317615·2HCl represents a new approach to antiangiogenic therapy in cancer-blocking multiple growth factor signaling pathways in endothelial cells with a single agent. 317615·HCl is in early clin. testing.

IT 365253-37-8, LY 317615
 RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU
 (Therapeutic use); BIOL (Biological study); USES (Uses)
 (antiangiogenic effects of a protein kinase C β -selective small
 mol.)
 RN 365253-37-8 CAPLUS
 CN 1H-Pyrrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-[1-(2-
 pyridinylmethyl)-4-piperidinyl]-1H-indol-3-yl]-, dihydrochloride (9CI)
 (CA INDEX NAME)



● 2 HCl

REFERENCE COUNT: 78 THERE ARE 78 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 14 OF 32 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 14
 ACCESSION NUMBER: 2001:319711 CAPLUS
 DOCUMENT NUMBER: 134:331632
 TITLE: Pharmaceutical compositions containing protein kinase
 C inhibitors and antioxidants
 INVENTOR(S): Cameron, Norman Eugene; Ways, Douglas Kirk
 PATENT ASSIGNEE(S): Eli Lilly and Co., USA
 SOURCE: PCT Int. Appl., 52 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001030331	A2	20010503	WO 2000-US26254	20001013
WO 2001030331	A3	20020124		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: US 1999-161129P P 19991022
 US 2000-177510P P 20000121

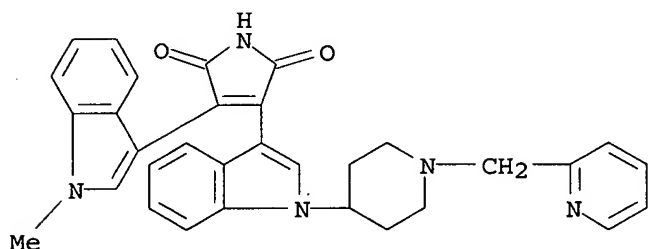
OTHER SOURCE(S): MARPAT 134:331632
 ED Entered STN: 04 May 2001

AB Compns. comprising a PKC inhibitor, or a salt and an antioxidant, essential fatty acid, or a prostacyclin agent, or a pharmaceutically acceptable salt thereof are provided. Also provided are methods of treatment comprising administration of such compns., and methods of treatment comprising co-administration of a PKC inhibitor, or a pharmaceutically acceptable salt thereof, and an antioxidant, essential fatty acid, or a prostacyclin agent, or a salt. Thus, an aerosol contained drug 0.35, EtOH 29.75, propellant-22 70.0%.

IT 170364-57-5
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (pharmaceutical compns. containing protein kinase C inhibitors and antioxidants)

RN 170364-57-5 CAPLUS

CN 1H-Pyrrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-[1-(2-pyridinylmethyl)-4-piperidinyl]-1H-indol-3-yl]- (9CI) (CA INDEX NAME)



L10 ANSWER 15 OF 32 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 15

ACCESSION NUMBER: 2002:195484 CAPLUS

DOCUMENT NUMBER: 137:210512

TITLE: Antiangiogenic and antitumor effects of a protein kinase C β inhibitor in human HT-29 colon carcinoma and human CaKil renal cell carcinoma xenografts

AUTHOR(S): Teicher, Beverly A.; Menon, Krishna; Alvarez, Enrique; Galbreath, Elizabeth; Shih, Chuan; Faul, Margaret M.

CORPORATE SOURCE: Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN, 46285, USA

SOURCE: Anticancer Research (2001), 21(5), 3175-3184
 CODEN: ANTRD4; ISSN: 0250-7005

PUBLISHER: International Institute of Anticancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 18 Mar 2002

AB The compound 317615·2HCl, a selective protein kinase C β inhibitor, was not very cytotoxic toward human CaKil renal cell carcinoma cells or human HT-29 colon carcinoma cells in monolayer culture. Isobologram anal. was used to determine additivity or synergy of the combination regimens. Exposure of CaKil cells to 317615·2HCl (10 or 100 mM) along with gemcitabine or 5-fluorouracil for 24 h resulted in cytotoxicity that appeared to be less-than-additive to additive for the 2 agents. Exposure of HT-29 cells to gemcitabine along with 317615·2HCl (10 or 100 mM) resulted in a synergistic cytotoxicity while combinations with 5-fluorouracil resulted in additive to greater-than-additive cytotoxicity for the agents. After treatment of CaKil or HT-29 xenograft-bearing mice with 317615·2HCl, immunohistochem. staining for expression of endothelial specific markers, either CD31 or CD105, was used to quantify the number of intratumoral vessels

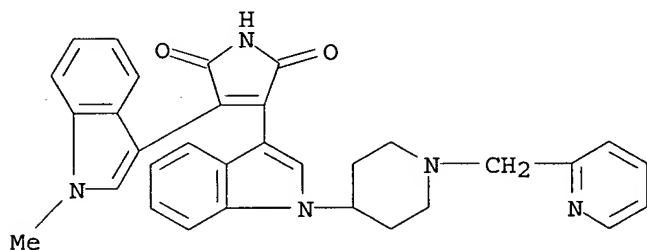
in the samples. CaKil tumor angiogenesis was very responsive to treatment with 317615·2HCl such that the number of intratumoral vessels stained by CD31 or CD105 was decreased to 20% of the control. The HT-29 colon carcinoma angiogenesis was also responsive to 317615·2HCl, such that the number of intratumoral vessels stained by CD31 or CD105 was decreased to 40 to 50% of the control. 5-Fluorouracil, cisplatin, or fractionated radiation therapy was combined with treatment with 317615·2HCl in the simultaneous combination treatment regimen in animals bearing HT-29 colon carcinoma xenografts. The resulting tumor growth delays indicated that administration of 317615·2HCl increased the effects of the cytotoxic therapy. Both a simultaneous or an overlapping treatment regimen and a sequential treatment regimen were used to assess 317615·2HCl alone and along with fractionated radiation therapy or gemcitabine against the human CaKil renal cell carcinoma xenograft. The CaKil tumor was quite sensitive to fractionated radiation therapy and to gemcitabine and, although 317615·2HCl was an effective single agent in this tumor, the combination regimens did not reach additivity for the combination regimens in vivo. 317615·2HCl is in early clin. testing.

IT 365253-37-8

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiangiogenic and antitumor effects of a protein kinase C β inhibitor in colon and renal cell carcinoma)

RN 365253-37-8 CAPLUS

CN 1H-Pyrrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-[1-(2-pyridinylmethyl)-4-piperidinyl]-1H-indol-3-yl]-, dihydrochloride (9CI)
(CA INDEX NAME)



● 2 HCl

REFERENCE COUNT: 70 THERE ARE 70 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 16 OF 32 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 16

ACCESSION NUMBER: 2001:307394 CAPLUS

DOCUMENT NUMBER: 135:282776

TITLE: Antiangiogenic and antitumor effects of a protein kinase C β inhibitor in human T98G glioblastoma multiforme xenografts

AUTHOR(S): Teicher, Beverly A.; Menon, Krishna; Alvarez, Enrique; Galbreath, Elizabeth; Shih, Chuan; Faul, Margaret

CORPORATE SOURCE: Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN, 46285, USA

SOURCE: Clinical Cancer Research (2001), 7(3), 634-640
CODEN: CCREF4; ISSN: 1078-0432

PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

ED Entered STN: 02 May 2001

AB Although rare, the morbidity and mortality from brain tumors are significant. Chemotherapy has made only a small impact on these tumors. The human T98G glioblastoma multiforme cell line was used as a brain tumor model. The protein kinase C β inhibitor 317615 \cdot 2HCl was not highly cytotoxic toward T98G cells in culture and was additive in cytotoxicity with carmustine (BCNU). When nude mice bearing s.c. T98G tumors were treated with 317615 \cdot 2HCl p.o. twice daily on days 14-30 after tumor cell implantation, the number of intratumoral vessels stained by CD31 was decreased to 37% of control, and the number of intratumoral vessels stained by CD105 was decreased to 50% of control. The compound 317615 \cdot 2HCl was an active antitumor agent against s.c. growing T98G xenografts. A treatment regimen administering 317615 \cdot 2HCl before, during, and after BCNU was compared with a treatment regimen administering 317615 \cdot 2HCl sequentially after BCNU. In the tumor growth delay determination of the s.c. tumor, the sequential treatment regimen was more effective than the simultaneous treatment regimen. However, when the same treatments were administered to animals bearing intracranial T98G tumors, the survival of animals receiving the simultaneous treatment regimen increased from 41 days for those treated with BCNU alone to 102 days for animals treated with the combination, whereas animals receiving the sequential treatment regimen survived 74 days. Treatment with the protein kinase C β inhibitor decreased T98G glioblastoma multiforme angiogenesis and improved treatment outcome with BCNU.

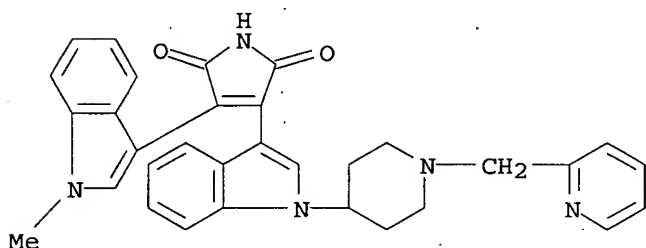
IT 365253-37-8

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(antiangiogenic and antitumor effects of PKC β inhibitor 317615 \cdot 2HCl)

RN 365253-37-8 CAPLUS

CN 1H-Pyrrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-[1-(2-pyridinylmethyl)-4-piperidinyl]-1H-indol-3-yl]-, dihydrochloride (9CI)
(CA INDEX NAME)



● 2 HCl

REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 17 OF 32 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 17
ACCESSION NUMBER: 2001:855440 CAPLUS
DOCUMENT NUMBER: 137:195076

Searched by Barb O'Bryen, STIC 2-2518

TITLE: Antiangiogenic and antitumor effects of a protein kinase C β inhibitor in murine Lewis lung carcinoma and human Calu-6 non-small-cell lung carcinoma xenografts

AUTHOR(S): Teicher, Beverly A.; Menon, Krishna; Alvarez, Enrique; Galbreath, Elizabeth; Shih, Chuan; Faul, Margaret M.

CORPORATE SOURCE: Lilly Corporate Center, Lilly Research Laboratories, Indianapolis, IN, 46285, USA

SOURCE: Cancer Chemotherapy and Pharmacology (2001), 48(6), 473-480
CODEN: CCPHDZ; ISSN: 0344-5704

PUBLISHER: Springer-Verlag

DOCUMENT TYPE: Journal

LANGUAGE: English

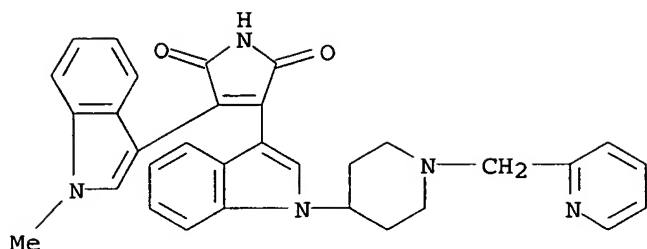
ED Entered STN: 27 Nov 2001

AB The compound 317615-2HCl, a potent inhibitor of VEGF-stimulated human umbilical vein endothelial cell proliferation, was not very effective against cultured Calu-6 non-small-cell lung carcinoma cells (IC₅₀ 26 μ M). Exposure of cultured Calu-6 cells to combinations of paclitaxel or carboplatin with 317615-2HCl resulted in cell survival that reflected ranges of less-than-additivity to additivity of the two agents. Administration of 317615-2HCl orally twice daily to nude mice bearing s.c. Calu-6 tumors resulted in a decrease of intratumoral vessels to 50% of the number in control tumors. 317615-2HCl showed antitumor activity against the Lewis lung carcinoma and increased the tumor growth delay produced by paclitaxel by 5-fold, that produced by gemcitabine by 2-fold and that produced by carboplatin by 1.7-fold. There was a decrease in the number of lung metastases in the Lewis lung carcinoma that paralleled the increased response of the primary tumor to each treatment combination. Administration of 317615-2HCl also increased the tumor growth delay produced by fractionated radiation therapy of the Lewis lung tumor. Treatment with 317615-2HCl was an effective therapy in the Calu-6 non-small-cell lung carcinoma xenograft when the compound was administered either early (days 4-18) or later (days 14-30) after transplantation. Combination treatment regimens in which 317615-2HCl was administered along with or sequentially with paclitaxel or carboplatin were much more effective than the agents administered alone. 317615-2HCl is in early clin. testing.

IT 365253-37-8
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiangiogenic and antitumor effects of protein kinase C β inhibitor 317615 in murine lung carcinoma and human non-small-cell lung carcinoma xenografts)

RN 365253-37-8 CAPLUS

CN 1H-Pyrrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-[1-(2-pyridinylmethyl)-4-piperidinyl]-1H-indol-3-yl]-, dihydrochloride (9CI)
(CA INDEX NAME)



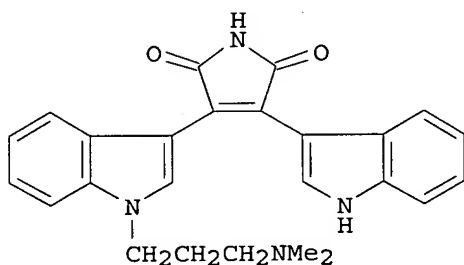
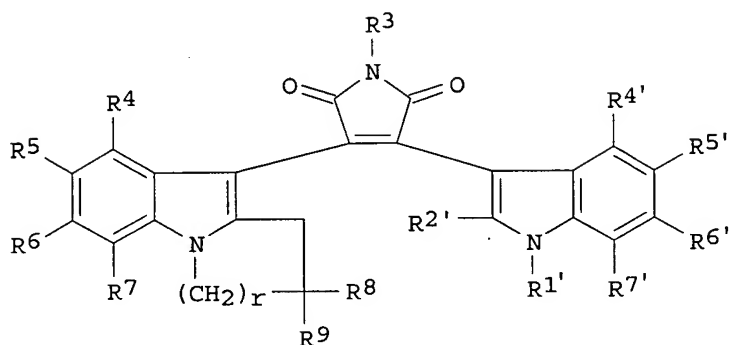
● 2 HCl

REFERENCE COUNT: 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 18 OF 32 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 18
 ACCESSION NUMBER: 1996:546509 CAPLUS
 DOCUMENT NUMBER: 125:275642
 TITLE: Preparation of bis(3-indolyl)maleimide inhibitors of protein kinase C β -1 and β -2 isoenzymes
 INVENTOR(S): Heath, William F., Jr.; Mcdonald, John H., III; Paal, Michael; Ruehter, Gerd; Schotten, Theo; Stenzel, Wolfgang
 PATENT ASSIGNEE(S): Eli Lilly and Company, USA
 SOURCE: U.S., 32 pp., Cont.-in-part of U.S. Ser. No. 173,741, abandoned.
 CODEN: USXXAM
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5545636	A	19960813	US 1994-324948	19941018
CA 2179650	AA	19950629	CA 1994-2179650	19941214
WO 9517182	A1	19950629	WO 1994-US14313	19941214
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UZ, VN				
RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9513398	A1	19950710	AU 1995-13398	19941214
JP 09507066	T2	19970715	JP 1995-517479	19941214
EP 817627	A1	19980114	EP 1995-904892	19941214
EP 817627	B1	20050309		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT				
EP 1449529	A1	20040825	EP 2004-102054	19941214
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT				
AT 290378	E	20050315	AT 1995-904892	19941214
ES 2236702	T3	20050716	ES 1995-904892	19941214
PT 817627	T	20050729	PT 1995-904892	19941214
ZA 9410139	A	19960620	ZA 1994-10139	19941220

US 5661173	A	19970826	US 1995-450320	19950525
US 5668152	A	19970916	US 1995-452617	19950525
US 5672618	A	19970930	US 1995-452606	19950525
HK 1008183	A1	20051230	HK 1998-109161	19980714
JP 2005225895	A2	20050825	JP 2005-135896	20050509
JP 2005225896	A2	20050825	JP 2005-135900	20050509
PRIORITY APPLN. INFO.:			US 1993-173741	B2 19931223
			US 1994-324948	A 19941018
			EP 1995-904892	A3 19941214
			JP 1995-517479	A3 19941214
			WO 1994-US14313	W 19941214
OTHER SOURCE(S):			MARPAT 125:275642	
ED Entered STN: 13 Sep 1996				
GI				



AB The title compds. [I; R1' = H, alkyl, (un)substituted aminoalkyl; R2' = H, alkyl, alkoxyalkyl, hydroxyalkyl, alkylthio, CF3, alkylsulfenyl; R3 = H, MeCO; R4-R7, R4'-R7' = H, halogen, alkyl, OH, alkoxy, alkoxy carbonyl, NO2, NH2, acetylamino, etc.; R8 = (CH2)sR10; R9 = (CH2)sR11; R10, R11 = OH, alkoxy, CO2H, (un)substituted NH2, N3, CN, etc.; r = 1-3; s = 0-3], which are selective inhibitors of protein kinase C isoenzymes beta-1 and beta-2, and which are therapeutically useful in treating conditions associated with diabetes mellitus (no data) and its complications, are prepared and

I-containing

formulations presented. Thus, indole derivative II was prepared and demonstrated a protein kinase C IC50 of 0.05 μ M both for the β -1 and the β -2 isoenzymes.

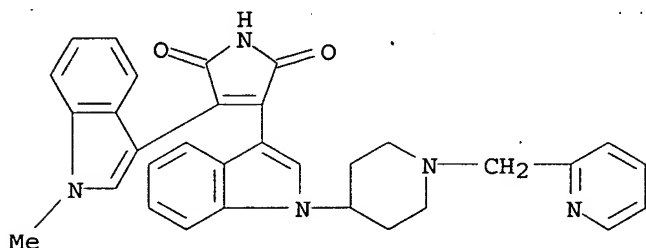
IT 170364-57-5P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);

BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of bis(3-indolyl)maleimide inhibitors of protein kinase C
 β -1 and β -2 isoenzymes)

RN 170364-57-5 CAPLUS

CN 1H-Pyrrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-[1-(2-pyridinylmethyl)-4-piperidinyl]-1H-indol-3-yl]- (9CI) (CA INDEX NAME)



L10 ANSWER 19 OF 32 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:859443 CAPLUS

DOCUMENT NUMBER: 143:26446

TITLE: A radiolabeled synthesis of [indole-C-14] LY317615, a PKC inhibitor

AUTHOR(S): Kennington, John W., Jr.; O'Bannon, Douglas D.

CORPORATE SOURCE: Lilly Research Laboratories, A Division of Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN, 46285, USA

SOURCE: Synthesis and Applications of Isotopically Labelled Compounds, Proceedings of the International Symposium, 8th, Boston, MA, United States, June 1-5, 2003 (2004), Meeting Date 2003, 305-307. Editor(s): Dean, Dennis C.; Filer, Crist N.; McCarthy, Keith E. John Wiley & Sons Ltd.: Chichester, UK.
CODEN: 69FZAZ; ISBN: 0-470-86365-X

DOCUMENT TYPE: Conference

LANGUAGE: English

ED Entered STN: 18 Oct 2004

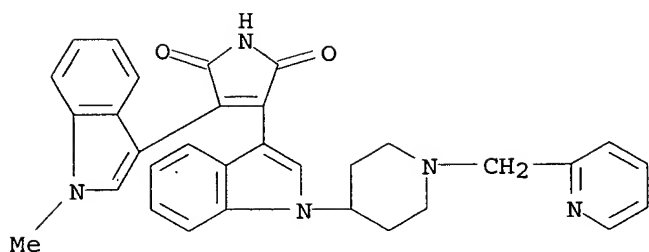
AB A radiolabeled synthesis of [indole-C-14]-LY317615, a Protein Kinase C inhibitor currently in clin. trial, is presented. The radiolabel is desired to be in a metabolically robust position and therefore the N-methylindole portion of the mol. was chosen. The synthetic route involves the preparation of C-14 radiolabeled indole in the two position utilizing the Fukuyama indole synthesis and coupling with the "Eastern" piece to complete the synthesis.

IT 365253-37-8P, LY317615

RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of carbon-14 labeled indole LY317615)

RN 365253-37-8 CAPLUS

CN 1H-Pyrrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-[1-(2-pyridinylmethyl)-4-piperidinyl]-1H-indol-3-yl]-, dihydrochloride (9CI)
(CA INDEX NAME)



●2 HCl

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 20 OF 32 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:645307 CAPLUS

DOCUMENT NUMBER: 139:337856

TITLE: Strategies for the synthesis of N-(azacycloalkyl)bisindolylmaleimides: selective inhibitors of PKC β

AUTHOR(S): Faul, Margaret M.; Grutsch, John L.; Kobierski, Michael E.; Kopach, Michael E.; Krumrich, Christine A.; Staszak, Michael A.; Udodong, Uko; Vicenzi, Jeffrey T.; Sullivan, Kevin A.

CORPORATE SOURCE: Lilly Corporate Center, Global Chemical Process Research and Development, Eli Lilly and Company, Indianapolis, IN, 46285-4813, USA

SOURCE: Tetrahedron (2003), 59(36), 7215-7229

CODEN: TETRAB; ISSN: 0040-4020

PUBLISHER: Elsevier Science B.V.

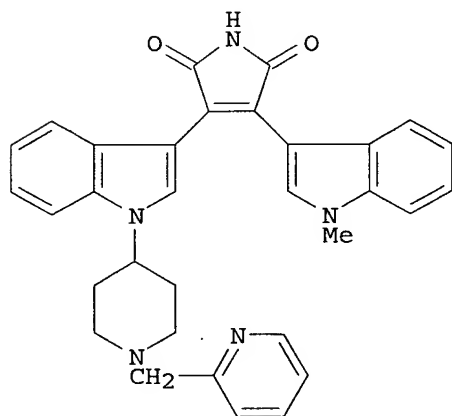
DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 139:337856

ED Entered STN: 19 Aug 2003

GI



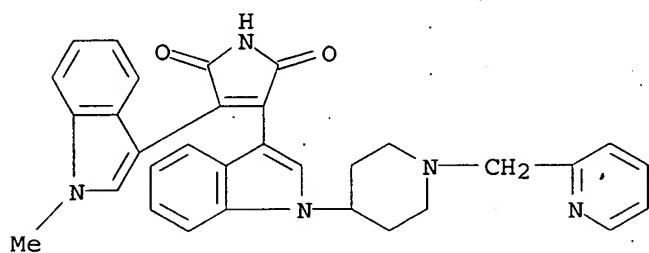
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AB N-(Azacycloalkyl)bisindolylmaleimides such as I have been identified to be selective inhibitors of PKC β . This manuscript will describe the synthetic approaches employed to prepare this class of compds. that resulted in development of efficient methods for preparation of N-(azacycloalkyl)indoles, indole-3-acetamides, and indole-3-glyoxylate esters.

IT 170364-57-5P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(N-(azacycloalkyl)bisindolylmaleimides for selective inhibition of PKC β)

RN 170364-57-5 CAPLUS

CN 1H-Pyrrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-[1-(2-pyridinylmethyl)-4-piperidinyl]-1H-indol-3-yl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 21 OF 32 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:363815 CAPLUS

DOCUMENT NUMBER: 139:230553

TITLE: Acyclic N-(azacycloalkyl)bisindolylmaleimides: isozyme selective inhibitors of PKC β

AUTHOR(S): Faul, Margaret M.; Gillig, James R.; Jirousek, Michael R.; Ballas, Lawrence M.; Schotten, Theo; Kahl, Astrid; Mohr, Michael

CORPORATE SOURCE: Global Chemical Process Research and Development Division, Lilly Research Laboratories, A Division of Eli Lilly and Company, Indianapolis, IN, 46285, USA

SOURCE: Bioorganic & Medicinal Chemistry Letters (2003), 13(11), 1857-1859
CODEN: BMCLE8; ISSN: 0960-894X

PUBLISHER: Elsevier Science B.V.

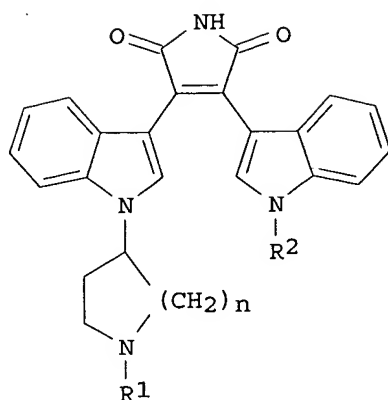
DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 139:230553

ED Entered STN: 13 May 2003

GI



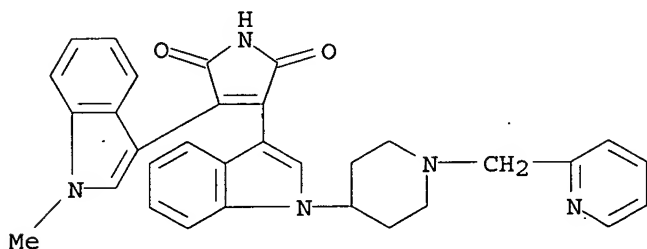
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AB The synthesis and structure-activity relationship (SAR) trends of a new class of N-(azacycloalkyl)bisindolylmaleimides, e.g. I (R1 = CH2-pyridyl, R2 = Me, n = 2), acyclic derivs. of staurosporine, is described. I exhibits an IC50 of 40-50 nM against the human PKCβ1 and PKCβ2 isoenzymes and selectively inhibits the PKCβ isoenzymes in comparison to other PKC isoenzymes (α, γ, δ, ε, ζ, and η). The series is also kinase selective for PKC in comparison to other ATP-dependent kinases. A comparison of the protein kinase C (PKC) isoenzyme and kinase activity of the series is made to the kinase inhibitor staurosporine.

IT **170364-57-5P**
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
 (preparation of acyclic N-(azacycloalkyl)bisindolylmaleimides as isoenzyme selective inhibitors of PKCβ)

RN 170364-57-5 CAPLUS

CN 1H-Pyrrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-[1-(2-pyridinylmethyl)-4-piperidinyl]-1H-indol-3-yl]- (9CI) (CA INDEX NAME)

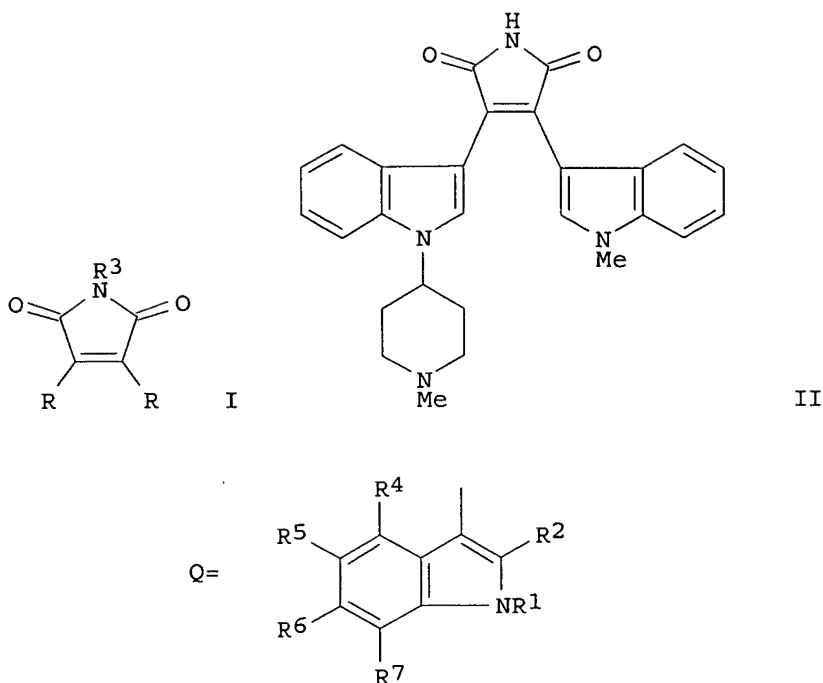


REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 22 OF 32 CAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1995:921902 CAPLUS
 DOCUMENT NUMBER: 123:339732
 TITLE: Preparation of bis(indolyl)pyrrolediones as protein kinase C inhibitors
 INVENTOR(S): Heath, William Francis Heath, Jr.; McDonald, John Hampton III; Paal, Michael; Ruether, Gerd; Schotten, Theo; Stenzel, Wolfgang

PATENT ASSIGNEE(S): Eli Lilly and Co., USA
 SOURCE: PCT Int. Appl., 104 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9517182	A1	19950629	WO 1994-US14313	19941214
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UZ, VN				
RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5545636	A	19960813	US 1994-324948	19941018
AU 9513398	A1	19950710	AU 1995-13398	19941214
JP 09507066	T2	19970715	JP 1995-517479	19941214
EP 817627	A1	19980114	EP 1995-904892	19941214
EP 817627	B1	20050309		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT				
AT 290378	E	20050315	AT 1995-904892	19941214
HK 1008183	A1	20051230	HK 1998-109161	19980714
PRIORITY APPLN. INFO.:			US 1993-173741	A 19931223
			US 1994-324948	A 19941018
			WO 1994-US14313	W 19941214
OTHER SOURCE(S): MARPAT 123:339732				
ED Entered STN: 16 Nov 1995				
GI				



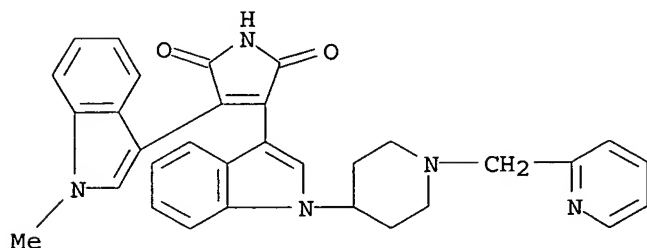
AB Title compds. [I; R = indolyl group Q; R¹ independently = H, (un)substituted alkyl, heterocyclyl(alkyl), etc.; R² independently = H, alkyl(thio), CF₃, etc.; 1 pair of R¹R² = (CH₂)XCH₂; R³ = H, Ac; R⁴-R⁷ independently = H, halo, alkyl, alkoxy, etc.; X = (un)substituted alkylene, (alkyl)imino, etc.; r = 1-3] were prepared Thus, 1-(1-methyl-4-piperidinyl)-1H-indole (preparation given) was cyclocondensed with iso-Pr 1-methyl-3-indolylacetimidate to give title compound II which had IC₅₀ of 0.02 and 0.01μM against β₁ and β₂ isoenzymes of protein kinase C, resp.

IT 170364-57-5P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of bis(indolyl)pyrrolediones as protein kinase C inhibitors)

RN 170364-57-5 CAPLUS

CN 1H-Pyrrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-[1-(2-pyridinylmethyl)-4-piperidinyl]-1H-indol-3-yl]- (9CI) (CA INDEX NAME)



L10 ANSWER 23 OF 32 USPATFULL on STN

Searched by Barb O'Bryen, STIC 2-2518

ACCESSION NUMBER: 2005:331346 USPATFULL
TITLE: Crystalline 2,5-dione-3-(1-methyl-1h-indol-3-yl)-4-[1-(pyridin-2-ylmethyl)piperidin-4-yl]-1h-pyrrole mono-hydrochloride
INVENTOR(S): Bush, Julie Kay, Fishers, IN, UNITED STATES
Faul, Margaret Mary, Zionsville, IN, UNITED STATES
Reutzel-Edens, Susan Marie, Zionsville, IN, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2005288332	A1	20051229
APPLICATION INFO.:	US 2003-520360	A1	20030708 (10)
	WO 2003-US19548		20030708
			20050105 PCT 371 date

	NUMBER	DATE
PRIORITY INFORMATION:	US 2003-395976P	20020712 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	ELI LILLY AND COMPANY, PATENT DIVISION, P.O. BOX 6288, INDIANAPOLIS, IN, 46206-6288, US	
NUMBER OF CLAIMS:	16	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	1 Drawing Page(s)	
LINE COUNT:	742	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to crystalline 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-(pyridin-2-yl-methyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole mono-hydrochloride salt, a pharmaceutical formulation containing said salt and to methods for treating cancer and for inhibiting tumor growth using said salt.

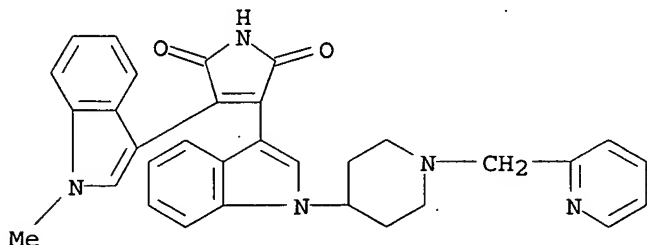
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT 170364-57-5P 359017-79-1P 647031-15-0P
(crystalline

3-(1-methyl-1H-indol-3-yl)-4-[1-(pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole-2,5-dione monohydrochloride preparation for antitumor pharmaceuticals)

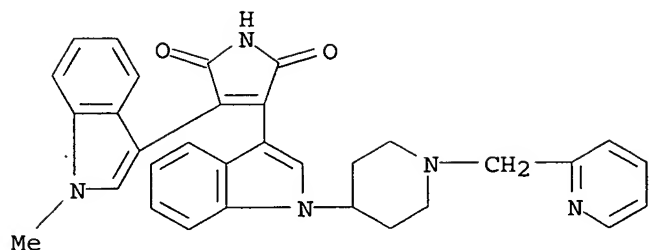
RN 170364-57-5 USPATFULL

CN 1H-Pyrrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-[1-(2-pyridinylmethyl)-4-piperidinyl]-1H-indol-3-yl]- (9CI) (CA INDEX NAME)



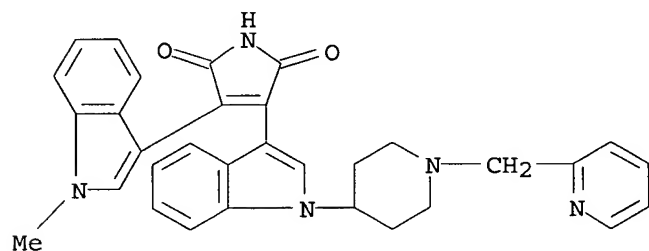
RN 359017-79-1 USPATFULL

CN 1H-Pyrrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-[1-(2-pyridinylmethyl)-4-piperidinyl]-1H-indol-3-yl]-, monohydrochloride (9CI)
(CA INDEX NAME)



● HCl

RN 647031-15-0 USPATFULL
 CN 1H-Pyrrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-[1-(2-pyridinylmethyl)-4-piperidinyl]-1H-indol-3-yl]-, monohydrochloride, monohydrate (9CI) (CA INDEX NAME)



● HCl

● H₂O

L10 ANSWER 24 OF 32 USPATFULL on STN
 ACCESSION NUMBER: 2005:240102 USPATFULL
 TITLE: Hydrogels used to deliver medicaments to the eye for the treatment of posterior segment diseases
 INVENTOR(S): Schultz, Clyde L., Ponte Vedra, FL, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2005208102	A1	20050922
APPLICATION INFO.:	US 2004-821718	A1	20040409 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2003-461354P	20030409 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	

LEGAL REPRESENTATIVE: FINCH IP LLC, P.O. BOX 1358, CONCORD, NH, 03302, US
 NUMBER OF CLAIMS: 20
 EXEMPLARY CLAIM: 1
 LINE COUNT: 502

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides a polymeric drug delivery system including a hydrogel containing one or more drugs for the treatment of a posterior segment disease. Allowing passive transference of this drug from a dilute solution into the hydrogel produces the delivery system. The hydrogel, when placed in contact with the eye, delivers the drug. The delivery of the drug is sustained over an extended period of time, which is of particular utility in the eye, which is periodically flushed with tears. This sustained delivery accelerates the treatment process while avoiding potential damaging effects of localized delivery of high concentrations of compounds, e.g., from eye drops.

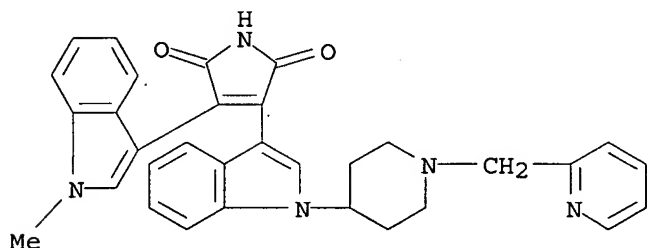
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT 365253-37-8, LY317615

(hydrogels containing drugs for treatment of eye diseases in posterior segment)

RN 365253-37-8 USPATFULL

CN 1H-Pyrrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-[1-(2-pyridinylmethyl)-4-piperidinyl]-1H-indol-3-yl]-, dihydrochloride (9CI)
 (CA INDEX NAME)



● 2 HCl

L10 ANSWER 25 OF 32 USPATFULL on STN

ACCESSION NUMBER: 97:88998 USPATFULL

TITLE: Protein kinase C inhibitors

INVENTOR(S): Heath, Jr., William F., Fishers, IN, United States
 McDonald, III, John H., Carmel, IN, United States
 Paal, Michael, Hamburg, Germany, Federal Republic of
 Schotten, Theo, Vierhofen, Germany, Federal Republic of
 Stenzel, Wolfgang, Reinbek, Germany, Federal Republic of

PATENT ASSIGNEE(S): Eli Lilly and Company, Indianapolis, IN, United States
 (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5672618		19970930
APPLICATION INFO.:	US 1995-452606		19950525 (8)
RELATED APPLN. INFO.:	Division of Ser. No. US 1994-324948, filed on 18 Oct 1994, now patented, Pat. No. US 5545636 which is a		

continuation-in-part of Ser. No. US 1993-173741, filed
on 23 Dec 1993, now abandoned

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Chang, Ceila
LEGAL REPRESENTATIVE: Caltrider, Steven P., Boone, David E., Collins, Daniel
W.
NUMBER OF CLAIMS: 6
EXEMPLARY CLAIM: 1
LINE COUNT: 2500

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention discloses compounds that are highly isozyme
selective protein kinase C beta-1 and beta-2 isozyme inhibitors.
Accordingly, the present invention provides a method of selectively
inhibiting protein kinase C isozymes beta-1, and beta-2. As isozyme
selective inhibitors of beta-1 and beta-2, the compounds are
therapeutically useful in treating conditions associated with diabetes
mellitus and its complications, as well as other disease states
associated with an elevation of the beta-1 and beta-2 isozyme.

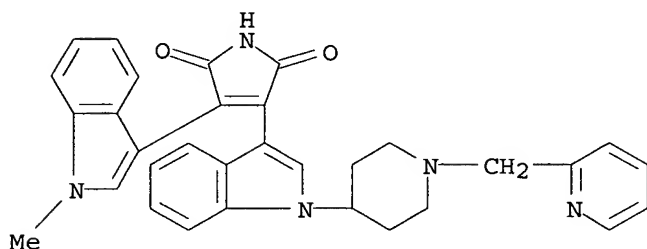
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT 170364-57-5P

(preparation of bis(indolyl)pyrrolediones as protein kinase C inhibitors)

RN 170364-57-5 USPTFULL

CN 1H-Pyrrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-[1-(2-
pyridinylmethyl)-4-piperidinyl]-1H-indol-3-yl]- (9CI) (CA INDEX NAME)



L10 ANSWER 26 OF 32 USPTFULL on STN

ACCESSION NUMBER: 97:83978 USPTFULL

TITLE: Protein kinase C inhibitors

INVENTOR(S): Heath, Jr., William F., Fishers, IN, United States
McDonald, III, John H., Carmel, IN, United States
Ruhter, Gerd, Hamburg, Germany, Federal Republic of
Schotten, Theo, Vierhofen, Germany, Federal Republic of
PATENT ASSIGNEE(S): Eli Lilly and Company, Indianapolis, IN, United States
(U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5668152		19970916
APPLICATION INFO.:	US 1995-452617		19950525 (8)
RELATED APPLN. INFO.:	Division of Ser. No. US 1994-324948, filed on 18 Oct 1994, now patented, Pat. No. US 5545636 which is a continuation-in-part of Ser. No. US 1993-173741, filed on 23 Dec 1993, now abandoned		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		

PRIMARY EXAMINER: Chang, Ceila
 LEGAL REPRESENTATIVE: Caltrider, Steven P., Boone, David E.
 NUMBER OF CLAIMS: 15
 EXEMPLARY CLAIM: 1
 LINE COUNT: 2300

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention discloses compounds that are highly isozyme selective protein kinase C beta-1 and beta-2 isozyme inhibitors. Accordingly, the present invention provides a method of selectively inhibiting protein kinase C isozymes beta-1, and beta-2. As isozyme selective inhibitors of beta-1 and beta-2, the compounds are therapeutically useful in treating conditions associated with diabetes mellitus and its complications, as well as other disease states associated with an elevation of the beta-1 and beta-2 isozyme.

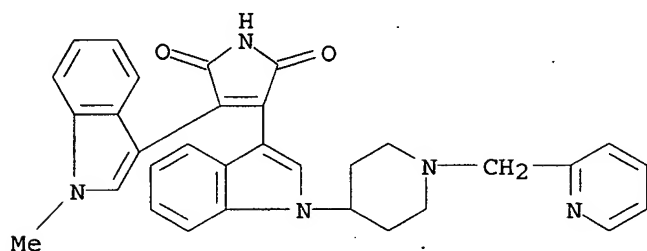
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT 170364-57-5P

(preparation of bis(indolyl)pyrrolediones as protein kinase C inhibitors)

RN 170364-57-5 USPATFULL

CN 1H-Pyrrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-[1-(2-pyridinylmethyl)-4-piperidinyl]-1H-indol-3-yl]- (9CI) (CA INDEX NAME)



L10 ANSWER 27 OF 32 USPATFULL on STN

ACCESSION NUMBER: 97:76155 USPATFULL

TITLE: Protein kinase C inhibitors

INVENTOR(S): Heath, Jr., William F., Fishers, IN, United States

McDonald, III, John H., Carmel, IN, United States

PATENT ASSIGNEE(S): Eli Lilly and Company, Indianapolis, IN, United States
 (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5661173		19970826
APPLICATION INFO.:	US 1995-450320		19950525 (8)
RELATED APPLN. INFO.:	Division of Ser. No. US 1994-324948, filed on 18 Oct 1994, now patented, Pat. No. US 5545636 And a continuation-in-part of Ser. No. US 1993-173741, filed on 23 Dec 1993, now abandoned		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Chang, Ceila		
LEGAL REPRESENTATIVE:	Caltrider, Steven P., Boone, David E.		
NUMBER OF CLAIMS:	4		
EXEMPLARY CLAIM:	1		
LINE COUNT:	2299		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention discloses compounds that are highly isozyme

selective protein kinase C beta-1 and beta-2 isozyme inhibitors. Accordingly, the present invention provides a method of selectively inhibiting protein kinase C isozymes beta-1, and beta-2. As isozyme selective inhibitors of beta-1 and beta-2, the compounds are therapeutically useful in treating conditions associated with diabetes mellitus and its complications, as well as other disease states associated with an elevation of the beta-1 and beta-2 isozyme.

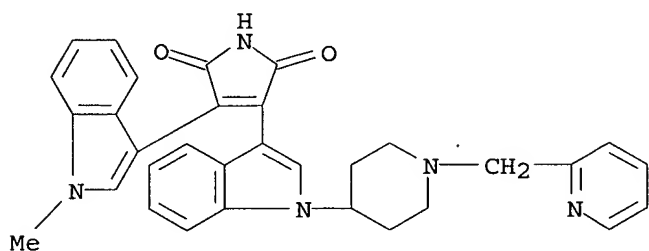
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT 170364-57-5P

(preparation of bis(indolyl)pyrrolediones as protein kinase C inhibitors)

RN 170364-57-5 USPATFULL

CN 1H-Pyrrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-[1-(2-pyridinylmethyl)-4-piperidinyl]-1H-indol-3-yl]- (9CI) (CA INDEX NAME)



L10 ANSWER 28 OF 32 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN

ACCESSION NUMBER: 2005-39670 DRUGU T S

TITLE: Results from phase II trial of enzastaurin (LY317615) in patients with recurrent high grade gliomas.

AUTHOR: Fine H A; Kim L; Royce C; Draper D; Haggarty I; Ellinzano H; Albert P; Kinney P; Musib L; Thornton D

CORPORATE SOURCE: Eli-Lilly

LOCATION: Bethesda, MD; Indianapolis, IN, USA

SOURCE: J.Clin.Oncol. (23, No. 16, Suppl., 1504, 2005)

CODEN: JCONDN ISSN: 0732-183X

AVAIL. OF DOC.: Neuro-Oncology Branch, NIG, Bethesda, Maryland, U.S.A.

LANGUAGE: English

DOCUMENT TYPE: Journal

ABSTRACT:

The antitumor activity of enzastaurin (LY-317615) was investigated in a phase II trial of 85 patients with recurrent high grade gliomas. Treatment was well tolerated with minimal hematologic and hepatotoxic drug-related toxicity. LY-317615 appears to have promising antitumoral activity against high-grade glioma. (conference abstract: 41st Annual Meeting of the American Society of Clinical Oncology, Orlando, Florida, USA, May 13-17, 2005).

SECTION HEADING: T Therapeutics
S Adverse Effects

CLASSIF. CODE: 35 Adverse Reactions
51 Chemotherapy - clinical
64 Clinical Trials

CONTROLLED TERM:

[01]

ENZASTAURIN *TR; ENZASTAURIN *AE; GLIOMA *TR; MARROW-DISEASE *AE; HEPATOPATHY *AE; ENCEPHALOPATHY *TR; NEOPLASM *TR; DR0109625 *RN; IN-VIVO *FT; CASES *FT; PHASE-II *FT; P.O. *FT; CYTOSTATIC *FT; CLIN.TRIAL *FT; ANGIOGENESIS-INHIBITORS *FT; CYTOSTATICS *FT; AKT-INHIBITORS *FT; APOPTOSIS-INDUCERS *FT; GLYCOGEN-SYNTHASE-KINASE-3-INHIBITORS *FT; PHOSPHOINOSITIDE-3-KINASE-INHIBITORS *FT; PROTEIN-KINASE-C-INHIBITORS *FT; TR *FT; AE *FT

CAS REGISTRY NO.: ~~1703645575~~

FIELD AVAIL.: AB; LA; CT

FILE SEGMENT: Literature

structures printed beginning on p. 51

L10 ANSWER 29 OF 32 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN

ACCESSION NUMBER: 2006-05209 DRUGU T P S

TITLE: A phase I dose-escalation study with oral LY317615 (L) in combination with capecitabine (C) in advanced cancer patients.

AUTHOR: Holden S; Britten C; Prager D; Finn R; Le M; Basche M; O'Bryant C; Levin A; Thornton D; Eckhardt S

CORPORATE SOURCE: Univ.Colorado; Univ.California; Lilly

LOCATION: Aurora, CO, Los Angeles, CA; Indianapolis, IN, USA

SOURCE: Eur.J.Cancer Suppl. (2, No. 8, 156, 2004) ISSN: 1359-6349

AVAIL. OF DOC.: University of Colorado Cancer Center, Developmental Therapeutics, Aurora, U.S.A.

LANGUAGE: English

DOCUMENT TYPE: Journal

ABSTRACT:

A phase I study was designed to evaluate the safety and pharmacokinetic behavior of p.o. LY-317615 and capecitabine in patients with advanced cancer. The schedule of LY-317615 and capecitabine was well tolerated. Stable disease was observed in some patients. PK analysis is pending in addition to biological analysis of ex vivo whole blood stimulation, both of which will be presented. Accrual is ongoing to establish the maximum tolerated dose of the combination, after which phase II studies are planned. (conference abstract: 16th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics, Geneva, Switzerland, September 28-October 1, 2004).

SECTION HEADING: T Therapeutics
P Pharmacology
S Adverse Effects

CLASSIF. CODE: 8 Pharmacokinetics
35 Adverse Reactions
51 Chemotherapy - clinical
64 Clinical Trials
73 Trial Preparations

CONTROLLED TERM:

ADVANCED *TR; PANCREAS *TR; PANCREOPATHY *TR; ARRHYTHMIA *AE; DIARRHEA *AE; NAUSEA *AE; COLON *TR; INTESTINE *TR; LUNG *TR; PNEUMOPATHY *TR; SARCOMA *TR; CARDIOPATHY *AE; GASTROENTEROPATHY *AE; NEOPLASM *TR; IN-VIVO *FT; CASES *FT; PHASE-I *FT; PHARMACOKINETICS *FT; CYTOSTATIC *FT; QT-INTERVAL *FT; HIGH *FT; LOW *FT; DOSAGE *FT; CLIN.TRIAL *FT; HEART *FT; ELECTROPHYSIOL. *FT

[01] ENZASTAURIN HYDROCHLORIDE *TR; ENZASTAURIN HYDROCHLORIDE *AE;
ENZASTAURIN HYDROCHLORIDE *DM; DR0050087 *RN; P.O. *FT;
ANGIOGENESIS-INHIBITORS *FT; CYTOSTATICS *FT; AKT-INHIBITORS
*FT; APOPTOSIS-INDUCERS *FT; GLYCOGEN-SYNTHASE-KINASE-3-
INHIBITORS *FT; PHOSPHOINOSITIDE-3-KINASE-INHIBITORS *FT;
PROTEIN-KINASE-C-INHIBITORS *FT; TR *FT; AE *FT; DM *FT
CAS REGISTRY NO.: 359017-79-1
[02] CAPECITABINE *TR; CAPECITABINE *AE; CAPECITABINE *DM;
DR9504617 *RN; P.O. *FT; METABOLITE *FT; PRODRUG *FT;
BIOPHARM. *FT; CYTOSTATICS *FT; SYNERGISTS *FT; TR *FT; AE
*FT; DM *FT
CAS REGISTRY NO.: 154361-50-9
[03] FLUOROURACIL *TR; FLUOROURACIL *AE; FLUOROURACIL *DM;
CORONARY-DISEASE *AE; VASOSPASM *AE; FLUOROURA *RN;
METABOLITE *FT; PRODRUG *FT; BIOSYNTH. *FT; BIOPHARM. *FT;
CYTOSTATICS *FT; THYMIDYLATE-SYNTHASE-INHIBITORS *FT; TR *FT;
AE *FT; DM *FT
CAS REGISTRY NO.: 51-21-8
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

L10 ANSWER 30 OF 32 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on
STN
ACCESSION NUMBER: 2003:474501 BIOSIS
DOCUMENT NUMBER: PREV200300474501
TITLE: Green chemistry approach to the synthesis of N-substituted
piperidones.
AUTHOR(S): Faul, Margaret M.; Kobierski, Michael E.; Kopach, Michael
E. [Reprint Author]
CORPORATE SOURCE: Lilly Research Laboratories, A Division of Eli Lilly and
Company, Chemical Process Research and Development
Division, Eli Lilly and Co., Indianapolis, IN, 46285-4813,
USA
kopach_michael@lilly.com
SOURCE: Journal of Organic Chemistry, (July 11 2003) Vol. 68, No.
14, pp. 5739-5741. print.
ISSN: 0022-3263 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 15 Oct 2003
Last Updated on STN: 15 Oct 2003

ABSTRACT: An efficient green chemistry approach to the synthesis of
N-substituted piperidones and piperidines was developed and applied to the
synthesis of 1-(2-pyridinyl-methyl)-piperidin-4-one, 1, a key starting material
for the synthesis of LY317615, an antiangiogenic agent currently under
development at Eli Lilly and Company. The general utility of this methodology,
which presents significant advantages over the classical Dieckman approach to
this class of compounds, was also demonstrated by the direct synthesis of a
series of substituted piperidones and piperidines, including potential dopamine
D4 receptor antagonists 2 and 3, that have been evaluated in the clinic as
antipsychotic agents.

CONCEPT CODE: Pathology - Therapy 12512
Pharmacology - General 22002

INDEX TERMS: Major Concepts
Methods and Techniques; Pharmacology

INDEX TERMS: Chemicals & Biochemicals
1-(2-pyridinyl-methyl)-piperidin-4-one; LY317615:
antiangiogenic agent, synthesis; N-substituted
piperidones: synthesis; dopamine D4 receptor;
piperidines: synthesis

INDEX TERMS: Methods & Equipment
green chemistry synthesis: laboratory techniques

REGISTRY NUMBER: ~~365253-37-8~~ (LY317615)
27154-43-4D (N-substituted piperidones)
110-89-4 (piperidines)

L10 ANSWER 31 OF 32 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on
STN

ACCESSION NUMBER: 2003:357635 BIOSIS
DOCUMENT NUMBER: PREV200300357635
TITLE: PKCbeta: A Rational Therapeutic Target in Diffuse Large
B-Cell Lymphoma.
AUTHOR(S): Wu, Erxi [Reprint Author]; Aguiar, Ricardo C. T. [Reprint
Author]; Savage, Kerry J. [Reprint Author]; Kutok, Jeffery
L. [Reprint Author]; Wang, FengFei [Reprint Author]; Aster,
Jon C. [Reprint Author]; Shipp, Margaret A. [Reprint
Author]
CORPORATE SOURCE: Department of Medicinal Oncology, Dana-Farber Cancer
Institute, Boston, MA, USA
SOURCE: Blood, (November 16 2002) Vol. 100, No. 11, pp. Abstract
No. 757. print.
Meeting Info.: 44th Annual Meeting of the American Society
of Hematology. Philadelphia, PA, USA. December 06-10, 2002.
American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 6 Aug 2003

Last Updated on STN: 6 Aug 2003

ABSTRACT: Diffuse large B-cell lymphoma (DLBCL), the most common lymphoid malignancy in adults, is curable in less than 50% of patients with conventional chemotherapy. We recently utilized oligonucleotide microarray gene expression profiles and supervised learning algorithms to develop a molecular predictor for DLBCL outcome (Nat. Med. 8:68, 2002). In the molecular model, one of the most prominently overexpressed genes in fatal/refractory DLBCLs was protein kinase C beta (PKCbeta). Further evidence linking overexpression of PKCbeta with outcome was obtained at a protein level by performing immunohistochemical (IHC) analysis of paraffin-embedded tumor tissue from the DLBCL pilot study patients. The alternatively-spliced PKCbeta1 and beta2 isoforms are the major PKC expressed by B-lymphocytes. These serine/threonine kinases have been implicated in critical phosphorylation pathways governing signal transduction, cellular proliferation and apoptosis, including BCR-dependent activation of NFkappaB. To credential PKCbeta as a possible rational therapeutic target in DLBCL, we assessed PKCbeta1 and beta2 transcripts, protein and enzymatic activity in a representative panel of DLBCL cell lines in the presence or absence of a PKCbeta-selective inhibitor that has already entered clinical trials (LY436881, test compound, LY317615, clinical trial compound). Four of the seven DLBCL cell lines had detectable to abundant PKCbeta transcripts by quantitative PCR and northern blotting and comparable PKC protein levels by western analysis. In the absence of exogenous signals, PKCbeta+ DLBCL cell lines also exhibited comparable enzymatic activity in in vitro kinase assays using a PKC-specific peptide substrate. In these in vitro kinase assays, LY436881 reduced PKC enzymatic activity to undetectable levels at doses that could be achieved in vivo. In PKCbeta+ DLBCL cell lines, the PKCbeta selective inhibitor also dramatically decreased proliferation (> 80% decrease, MTS assays) and increased apoptosis (22-70% apoptotic cells, annexin V/PI assays) at clinically achievable doses. In contrast, PKCbeta-negative DLBCL cell lines were largely resistant to the anti-proliferative and pro-apoptotic effects of

LY436881. To gauge the frequency of PKCbeta expression in the clinical setting in which the PKCbeta inhibitor might first be tested, 11 relapsed DLBCLs were evaluated for PKCbeta expression by immunohistochemistry. All of these relapsed tumors demonstrated abundant PKCbeta expression. Taken together, these data support further clinical analysis of PKCbeta as a rational therapeutic target in DLBCL. For these reasons, a multi-institutional phase II trial of the oral PKCbeta inhibitor, LY317615, has been initiated in patients with relapsed DLBCL.

CONCEPT CODE: General biology - Symposia, transactions and proceedings
00520

Cytology - Animal 02506

Cytology - Human 02508

Enzymes - General and comparative studies: coenzymes
10802

Pathology - Therapy 12512

Blood - Blood and lymph studies 15002

Blood - Blood cell studies 15004

Pharmacology - General 22002

Pharmacology - Clinical pharmacology 22005

Immunology - General and methods 34502

INDEX TERMS: Major Concepts

Blood and Lymphatics (Transport and Circulation);
Enzymology (Biochemistry and Molecular Biophysics);
Immune System (Chemical Coordination and Homeostasis);
Pharmacology

INDEX TERMS: Parts, Structures, & Systems of Organisms

B-lymphocyte: blood and lymphatics, immune system

INDEX TERMS: Chemicals & Biochemicals

LY317615: enzyme inhibitor-drug; LY436881: enzyme
inhibitor-drug; protein kinase C beta-1 isoform
[PKC-beta-1 isoform]: expression, regulation; protein
kinase C beta-2 isoform [PKC-beta-2 isoform]:
expression, regulation

INDEX TERMS: Miscellaneous Descriptors

cellular apoptosis; cellular proliferation;
phosphorylation pathway; signal transduction pathway

ORGANISM: Classifier

Hominidae 86215

Super Taxa

Primates; Mammalia; Vertebrata; Chordata; Animalia

Organism Name

human (common): patient

Taxa Notes

Animals, Chordates, Humans, Mammals, Primates,
Vertebrates

REGISTRY NUMBER: 365253-37-8 (LY317615)

L10 ANSWER 32 OF 32 PROUSDDR COPYRIGHT 2006 PROUS SCIENCE on STN

ACCESSION NUMBER: 2002:108 PROUSDDR

DOCUMENT NUMBER: 306147

CHEMICAL NAME: 3-(1-Methyl-1H-indol-3-yl)-4-(1-(1-(pyridin-2-
ylmethyl)piperidin-4-yl)-1H-indol-3-yl)-1H-pyrrole-2,5-
dione dihydrochloride

DRUG NAME: 317615.2HCl

LY-317615.2HCl

GENERIC NAME: Enzastaurin hydrochloride (Prop INNM, USAN)

CAS REGISTRY NUMBER: 359017-72-4

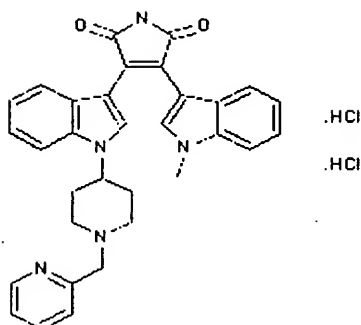
365253-37-8

170364-57-5 (free base)

359017-79-1 (monoHCl)

MOLECULAR FORMULA: C32 H31 Cl2 N5 O2
STATUS: Actively Investigated
HIGHEST DEV. PHASE: PHASE II
ORIGINATOR: Lilly
National Cancer Institute (US)
CLASSIFICATION CODE: Brain Cancer Therapy; Colorectal Cancer Therapy;
Non-Small Cell Lung Cancer Therapy; Non-Hodgkin's
Lymphoma Therapy; Solid Tumors Therapy; Antineoplastic
Enhancing Agents
ACTION MECHANISM: Angiogenesis Inhibitors; Inhibitors of Signal
Transduction Pathways
OTHER SOURCE: SYNTHLINE 2004000063
ENTRY DATE: Entered STN: 9 May 2004
Last Updated on STN: 1 Mar 2006

STRUCTURE:



PROUS REFERENCES:

RefID: 686322 (Text Available)
Drug Data Report, Vol. 24, No. 9, pp 841, 2002

REFERENCE TEXT:

RefID: 686322
ACTION - Selective, small-molecule inhibitor of protein kinase C β (PKC β ; IC₅₀ = 0.03 μ M) with selective growth-inhibitory activity against vascular endothelial growth factor (VEGF)-induced human umbilical vein endothelial cell (HUVEC) proliferation (IC₅₀ = 150 nM) relative to human tumor cells. It inhibited growth factor-stimulated neovascularization in the rat cornea micropocket assay when given at a dose of 10 mg/kg p.o. b.i.d. for 10 days. Moreover, compound produced marked inhibition of tumor vascularization in a range of human solid tumor xenografts and it was effective both as a single agent and in combination with cytotoxic therapies in brain, breast, ovarian, non-small cell lung, small cell lung, gastric, hepatocellular, colon and renal cell cancer xenografts. Additive activity was generally seen in combination with cytotoxic agents. Results of an ongoing phase I trial in patients with solid tumors receiving escalating single oral doses of compound (20-350 mg) showed no dose-limiting toxicity at up to 160 mg; the most frequent adverse event has been grade 1 fatigue. At these doses, the half-life of compound was 9-25 h, with no significant accumulation. Disease

stabilization was achieved in 4 of 27 patients treated with over 4 cycles, and 3 of these have received over 6 cycles.

PATENT REFERENCES:

TITLE: Protein kinase C inhibitors
INVENTOR(S): Paal, M.; Stenzel, W.; Schotten, T.; McDonald, J.H. I. I. I.; Heath, W.F.H. Jr.; Ruther, G.

PATENT ASSIGNEE(S): Lilly
PATENT INFORMATION: EP 817627 19980114
EP 1449529 20040825
JP 97507066 19970715
JP 2005225895 20050825
JP 2005225896 20050825
US 5545636 19960813
WO 9517182 19950629
PRIORITY INFORMATION: US 1993-173741 19931223
US 1994-324948 19941018

TITLE: Therapeutic compositions including protein kinase C inhibitors
INVENTOR(S): Cameron, N.E.; Ways, D.K.
PATENT ASSIGNEE(S): Lilly
PATENT INFORMATION: WO 2001030331 20010503
PRIORITY INFORMATION: US 1999-161129 19991022
US 2000-177510 20000121

TITLE: Use of a protein kinase C inhibitor to enhance the clinical efficacy of anti-neoplastic chemotherapeutic agents and radiation therapy
INVENTOR(S): Teicher, B.A.; Ways, D.K.
PATENT ASSIGNEE(S): Lilly
PATENT INFORMATION: WO 2002002094 20020110
PRIORITY INFORMATION: US 2000-215043 20000629

TITLE: Therapeutic treatment of cancer with a protein kinase C inhibitor
INVENTOR(S): Teicher, B.A.; Ways, D.K.
PATENT ASSIGNEE(S): Lilly
PATENT INFORMATION: WO 2002002116 20020110
PRIORITY INFORMATION: US 2000-215172 20000629

TITLE: Bisindolyl maleimides useful for treating prostate cancer and AKT-mediated diseases
INVENTOR(S): Graff, J.R.
PATENT ASSIGNEE(S): Lilly
PATENT INFORMATION: WO 2005041953 20050512
PRIORITY INFORMATION: US 2003-514291 20031024

TITLE: Protein kinase C inhibitors for the treatment of autoimmune diseases and of transplant rejection
INVENTOR(S): Schuler, W.; Wagner, J.
PATENT ASSIGNEE(S): Novartis
PATENT INFORMATION: WO 2005097108 20051020
PRIORITY INFORMATION: GB 2004-8066 20040408
GB 2004-14540 20040629
GB 2004-22068 20041005

REFERENCES:

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"Antiangiogenic effects and therapeutic potential of a protein kinase Cbeta inhibitor in preclinical models"
Teicher, B.A.; Alvarez, E.; Menon, K.; Gallbreath, E.; Shih, C.; Faul, M., Int J Antimicrob Agents, Vol. 17, No. Suppl. 1, (Abst S6.03), 2001
- (2) RefID: 626834, Periodic Publication
"Antiangiogenic and antitumor effects of a protein kinase Cbeta inhibitor in human T98G glioblastoma multiforme xenografts"
Teicher, B.A.; Menon, K.; Alvarez, E.; Galbreath, E.; Shih, C.; Faul, M., Clin Cancer Res, Vol. 7, No. 3, pp 634, 2001
- (3) RefID: 642764, Congress Literature
"Novel therapies for advanced non-small cell lung cancer: The combination of chemotherapy with biologic agents in the treatment of advanced disease"
Herbst, R.S., Chemother Found Symp Innov Cancer Chemother Tomorrow (19th Edition), Nov 7 2001-Nov 10 2001, New York, (Abst 59)
- (4) RefID: 643364, Congress Literature
"Phase I dose escalation and pharmacokinetic study of single-agent protein kinase C beta inhibitor, LY317615"
Herbst, R.S.; et al., AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther, Oct 29 2001-Nov 2 2001, Miami Beach, (Abst 29)
- (5) RefID: 653652, Periodic Publication
"Antiangiogenic and antitumor effects of a protein kinase Cbeta inhibitor in murine Lewis lung carcinoma and human Calu-6 non-small-cell lung carcinoma xenografts"
Teicher, B.A.; et al., Cancer Chemother Pharmacol, Vol. 48, No. 6, pp 473, 2001
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Teicher, B.A.; et al., Anticancer Res, Vol. 21, No. 5, pp 3175, 2001
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"Antiangiogenic efficacy and PK/PD modeling with a PKCbeta inhibitor in preclinical lung cancer models"
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"Antiangiogenic activity of a protein kinase Cbeta (PKCbeta) inhibitor"
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Keyes, K.; et al., Proc Am Assoc Cancer Res (AACR), Vol. 43, (Abst 133), 2002

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"Antiangiogenic effects of a protein kinase C β -selective small molecule"
Teicher, B.A.; et al., Cancer Chemother Pharmacol, Vol. 49, No. 1, pp 69, 2002
- (12) RefID: 670433, Periodic Publication
"Phase I study of LY317615, a protein kinase C β inhibitor"
Herbst, S.H.; Thornton, D.E.; Kies, M.S.; Sinha, V.; Flanagan, S.; Cassidy, C.A.; Carducci, M.A., Proc Am Soc Clin Oncol (ASCO), Vol. 21, No. Part 1, (Abst 326), 2002
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"Acyclic N-(azacycloalkyl)bisindolylmaleimides: Isozyme selective inhibitors of PKC β "
Faul, M.M.; Gillig, J.R.; Jirousek, M.R.; Ballas, L.M.; Schotten, T.; Kahl, A.; Mohr, M., Bioorg Med Chem Lett, Vol. 13, No. 11, pp 1857, 2003
- (15) RefID: 778789, Periodic Publication
"LY317615 decreases plasma VEGF levels in human tumor xenograft-bearing mice"
Keyes, K.A.; et al., Cancer Chemother Pharmacol, Vol. 53, No. 2, pp 133, 2004
- (16) RefID: 809133, Periodic Publication
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WHO Drug Inf, Vol. 18, No. 1, pp 54, 2004
- (17) RefID: 846553, Periodic Publication
"A phase I dose-escalation study with oral LY317615 (L) in combination with capecitabine (C) in advanced cancer patients"
Holden, S.; Britten, C.; Prager, D.; Finn, R.; Le, M.; Basche, M.; O'Bryant, C.; Levin, A.; Thornton, D.; Eckhardt, S., Eur J Cancer - Suppl, Vol. 2, No. 8, (Abst 156), 2004
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"Correlation between protein kinase C- β expression and patient survivals in primary tumors - implications for clinical drug development"
Li, D.; Phong, M.; Lahn, M.; Thornton, D.; Brail, L.; Ganji, G.; Liao, B., Eur J Cancer - Suppl, Vol. 2, No. 8, (Abst 174), 2004
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"The protein kinase C β (PKC β) inhibitor enzastaurin HCl (LY317615) augments chemosensitivity of multiple myeloma (MM) cells to dexamethasone and the proteasome inhibitor bortezomib"
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Graff, J.R.; et al., Int Symp Target Anticancer Ther (3rd Edition),

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"Results from phase II trial of Enzastaurin (LY317615) in patients with recurrent high grade gliomas"
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"Enzastaurin HCl (LY317615) suppresses GSK3beta phosphorylation, induces apoptosis and suppresses growth of human colon cancer and glioblastoma xenografts"
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"A phase II study of enzastaurin, a protein kinase C-beta (PKCbeta) inhibitor, in the treatment of relapsed diffuse large B-cell lymphoma (DLBCL)"
Robertson, M.; Kahl, B.; Vose, J.; et al., Blood, Vol. 106, No. 11, (Abst 934), 2005
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"The PKCbeta selective inhibitor, enzastaurin (LY317615), inhibits growth of human lymphoma cells"
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- (25) RefID: 948117, Periodic Publication
"Inhibition of protein kinase C beta by enzastaurin (LY 317615) induces alterations of key regulators of cell cycle and apoptosis in mantle cell lymphoma and synergizes with chemotherapeutic agents in a sequence dependent manner"
Rieken, M.; et al., Blood, Vol. 106, No. 11, (Abst 2416), 2005
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"The PKC- inhibitor enzastaurin inhibits MM cell growth, survival and migration in the bone marrow microenvironment"
Podar, K.; et al., Blood, Vol. 106, No. 11, (Abst 1584), 2005
- (28) RefID: 959759, Congress Literature
"Evaluation of in vitro synergistic anti-tumor activity of enzastaurin and alimta against thyroid cancer cell lines"
Oberschmidt, O.; Eismann, U.; Schulz, L.; Struck, S.; Blatter, J.; Lahn, M.M.; Ma, D.; Hanauske, A.-R., AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther, Nov 14 2005-Nov 18 2005, Philadelphia, (Abst B6)

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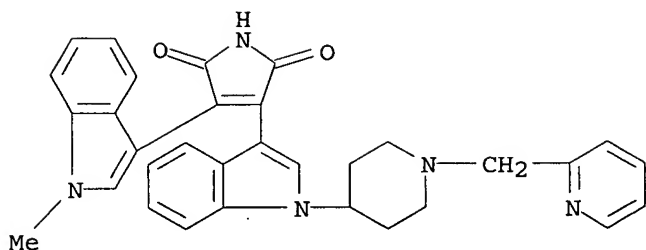
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*structures for hits
from DrugK & Bids13*

L7 ANSWER 1 OF 4 REGISTRY COPYRIGHT 2006 ACS on STN
RN ~~6470364-57-5~~ REGISTRY
ED Entered STN: 06 Feb 2004
CN 1H-Pyrrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-[1-(2-
pyridinylmethyl)-4-piperidinyl]-1H-indol-3-yl]-, monohydrochloride,
monohydrate (9CI) (CA INDEX NAME)
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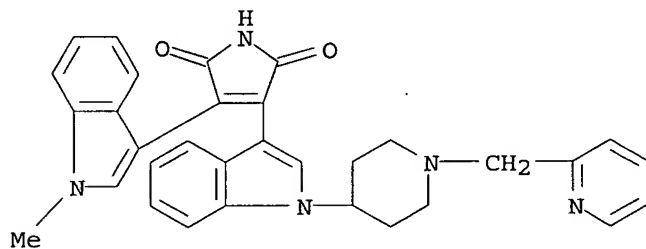


● HCl

● H₂O

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L7 ANSWER 2 OF 4 REGISTRY COPYRIGHT 2006 ACS on STN
RN 365253-37-8 REGISTRY
ED Entered STN: 29 Oct 2001
CN 1H-Pyrrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-[1-(2-pyridinylmethyl)-4-piperidinyl]-1H-indol-3-yl]-, dihydrochloride (9CI)
(CA INDEX NAME)
OTHER NAMES:
CN LY 317615
DR 359017-72-4
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SR CA
LC STN Files: BIOSIS, CA, CAPLUS, IMSRESEARCH, PROUSDDR, SYNTHLINE,
TOXCENTER, USPATFULL
CRN (170364-57-5)



●2 HCl

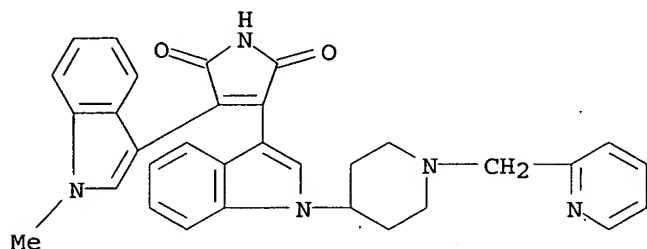
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RN 359017-79-1 REGISTRY

ED Entered STN: 27 Sep 2001
CN 1H-Pyrrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-[1-(2-pyridinylmethyl)-4-piperidinyl]-1H-indol-3-yl]-, monohydrochloride (9CI)
(CA INDEX NAME)

OTHER NAMES:

CN Enzastaurin hydrochloride
MF C32 H29 N5 O2 . Cl H
SR CAS Client Services
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SYNTHLINE, TOXCENTER, USAN, USPATFULL
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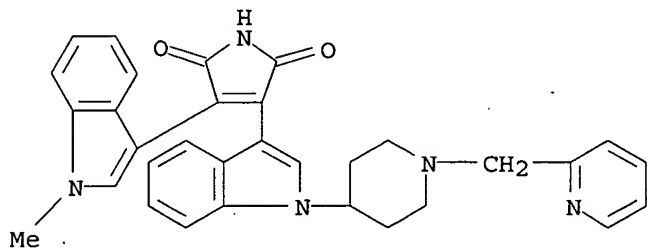


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ED Entered STN: 17 Nov 1995
CN 1H-Pyrrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-[1-(2-pyridinylmethyl)-4-piperidinyl]-1H-indol-3-yl]- (9CI) (CA INDEX NAME)

OTHER NAMES:

CN Enzastaurin
FS 3D CONCORD
MF C32 H29 N5 O2
CI COM
SR CA
LC STN Files: ADISINSIGHT, CA, CAPLUS, CASREACT, DDFU, DRUGU, IMSDRUGNEWS,
IMSRESEARCH, PROMT, PROUSDDR, SYNTHLINE, TOXCENTER, USAN, USPATFULL



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OR 359017-79-1/BI OR 41661-47-6/BI OR 616898-64-7/BI OR
647031-15-0/BI OR 647031-16-1/BI OR 6959-47-3/BI)
D SCAN
L5 STRUCTURE UPLOADED
L6 0 SEA SSS SAM L5
D L4
D L5
L7 4 SEA SSS FUL L5
SAVE TEMP L6 QAZ360FULL/A

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L8 22 SEA ABB=ON L7

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L10 32 DUP REM L9 (22 DUPLICATES REMOVED)
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ANSWERS '23-27' FROM FILE USPATFULL
ANSWERS '28-29' FROM FILE DRUGU
ANSWERS '30-31' FROM FILE BIOSIS
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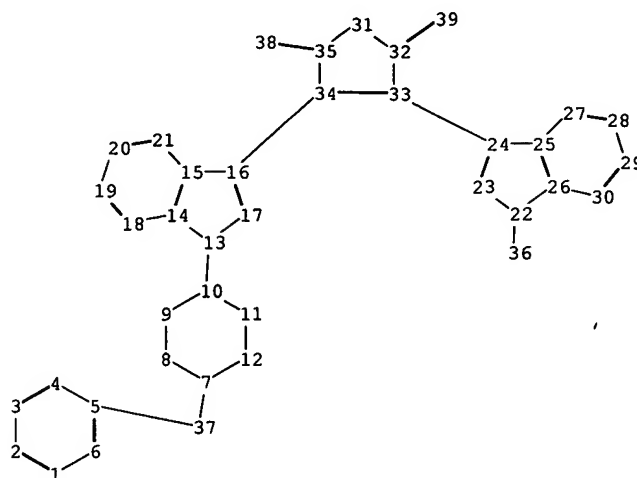
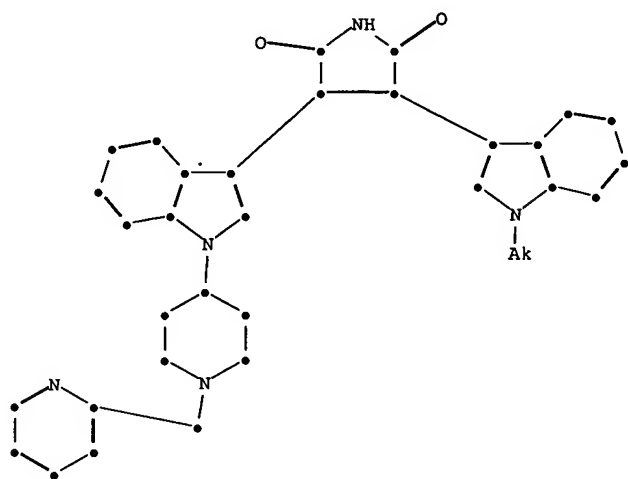
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chain nodes :

36 37 38 39

ring nodes :

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
22 23 24 25 26 27 28 29 30 31 32 33 34 35

chain bonds :

5-37 7-37 10-13 16-34 22-36 24-33 32-39 35-38

ring bonds :

1-2 1-6 2-3 3-4 4-5 5-6 7-8 7-12 8-9 9-10 10-11 11-12 13-14
13-17 14-15 14-18 15-16 15-21 16-17 18-19 19-20 20-21 22-23
22-26 23-24 24-25 25-26 25-27 26-30 27-28 28-29 29-30 31-32
31-35 32-33 33-34 34-35

exact/norm bonds :

7-37 10-13 13-14 13-17 15-16 16-17 22-23 22-26 22-36 23-24
24-25 31-32 31-35 32-33 32-39 33-34 34-35 35-38

exact bonds :

5-37 7-8 7-12 8-9 9-10 10-11 11-12 16-34 24-33

normalized bonds :

1-2 1-6 2-3 3-4 4-5 5-6 14-15 14-18 15-21 18-19 19-20 20-21
25-26 25-27 26-30 27-28 28-29 29-30

Connectivity :

36:1 E exact RC ring/chain

Match level :

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom
10:Atom 11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom
18:Atom 19:Atom 20:Atom 21:Atom 22:Atom 23:Atom 24:Atom 25:Atom
26:Atom

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27:Atom 28:Atom 29:Atom 30:Atom 31:Atom 32:Atom 33:Atom
34:Atom 35:Atom 36:CLASS 37:CLASS 38:CLASS 39:CLASS

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